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SYNTHESIS AND ANALYSIS OF THREE-DIMENSIONAL
MOLECULAR ARCHITECTURES

A Thesis

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirements for a degree of
Master of Science

in

The Department of Chemistry

by
Patricia Beck
B.A. Ripon College, 1998
December, 2001

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Abstract

The use of resorcinarenes in the study of biologically significant phenomena has been the focus of much attention, due to the versatility of these macrocyclic compounds. In this thesis, two applications of resorcinarenes are explored. First, the search for the mechanism by which tetraarylboronic acid resorcinarenes lead to colorimetric detection and quantization of saccharide analyte concentration in solution is described. Second, the extension of the lower rim conjugation of the resorcinarene macrocycle by the fourfold addition of various length oligo(*p*-phenylene) rods is discussed. The synthesis of these tubular materials, with potential uses as artificial ion channels and for binding and transportation of large molecular guests, is the primary focus of this work.

Chapter 1. Introduction

Description of Intent

First reported by Adolf von Baeyer in 1872 as part of his effort to develop new dyes,^{1,2} the resorcinarenes are a class of cyclic aromatic tetramers that result from the acid-catalyzed condensation of resorcinol with various aldehydes. Although resorcinarenes were initially synthesized more than 125 years ago, the exact structure of these macrocyclic molecules was not confirmed until Erdtman and coworkers were able to perform a single crystal X-ray analysis in 1968.^{3,4} Since that time, four different three-dimensional resorcinarene isomers have been found experimentally.⁵ The two stereoisomers (C_{4v} and C_{2h}) which will appear several times throughout this work along with important structural features are shown in Fig. 1.1.

Resorcinarenes have influenced the fields of molecular recognition,^{6,7} materials science,⁵ and supramolecular chemistry.⁶ A plethora of potential applications for these molecules have been studied or proposed, including chemosensing,⁵ catalysis, energy storage,⁷ drug delivery,⁷ and artificial ion channels.⁸ The tetraarylboronic acid resorcinarenes synthesized in this research group are known to bind sugars, sugar phosphates, and other biomolecules in solution, which allows for the concentration of the saccharide to be determined using UV-Visible spectroscopy.^{9,10} In this thesis, the ability

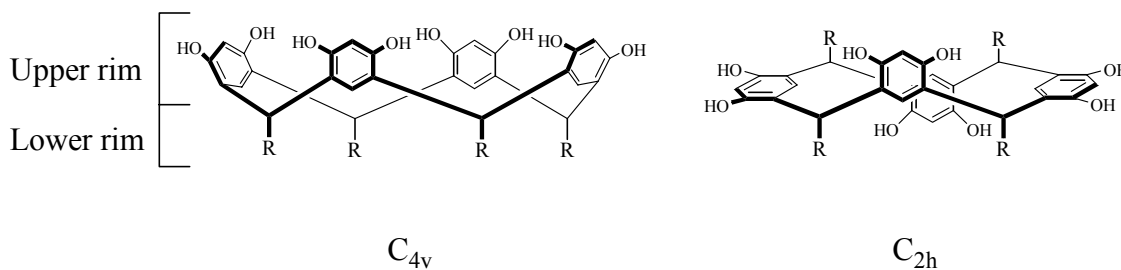


Fig. 1.1. Structure of the C_{4v} (rccc) and C_{2h} (rctt) resorcinarene isomers and key structural features. R is derived from the aldehyde and may be aliphatic or aromatic.

of the resorcinarene macrocycles to act as sensors for a variety of analytes, as well as templates for the synthesis of robust, shape-persistent tubular molecules, is investigated.

Sugars and sugar phosphates participate in many biological processes¹¹ such as glycolysis (production of energy from glucose) and amino acid synthesis. Consequently, sugar identification and quantification in human blood and other biological samples is of the utmost importance. Since sugars do not possess chromophoric moieties, current colorimetric tests for saccharides all depend on indirect methods. Previous nonenzymatic assays for detecting reducing sugars, such as the Nelson-Somogyi method,¹² employ toxic reagents and corrosive sulfuric acid. Additionally, these tests are not selective for one particular sugar in the presence of other saccharides. For example, the relatively low levels of fructose in human plasma cannot be determined reliably by conventional methods due primarily to the presence of excess glucose.¹³ In the presence of 100 equivalents of glucose, however, we are able to measure the concentration of fructose (fructose concentration = 5.2 mM, glucose concentration = 0.52 M) using our resorcinarene sensor molecule by monitoring the UV-Vis spectrum of the sample at 464 nm.¹⁴ Thus, our resorcinarene macrocycles are powerful and selective sugar sensors.

Separately, both resorcinarenes and oligophenylenes have been utilized in ion channel research with some success.^{15,16,17,18} Resorcinarenes with long alkyl chains, for example, are known to selectively allow the transport of K^+ ions (versus Na^+ , Rb^+ , and Cs^+ ions) across a lipid bilayer.¹⁵ In addition to acting as a selective pore opening, resorcinarene macrocycles offer the advantage of a well-defined 7 Å cavity diameter⁵ and, therefore, possess the potential to create a channel to allow the transport of small molecules across a membrane. Likewise, oligophenylene rods with various side-chains

can self-assemble to form ion channels long enough to span a cellular lipid bilayer.^{16,17,18} Oligophenylenes are ideal for such applications, since these rod-like compounds can be synthesized with a definite length and a plethora of side groups including amino acids,^{17,18} amines, methyls, alkenes, and crown ethers.¹⁶ The need for the rods to self-assemble into a tube, however, has been a significant impediment, because the number of rods that will assemble and, consequently, the cavity diameter of the tube is difficult to control and predict. By attaching oligophenylene rods to a resorcinarene scaffold, we envision a tubular material with both a definite cavity diameter and length. Additionally, the resorcinarene-oligophenylene compounds may possess some of the properties, such as the ion selectivity of resorcinarenes, that resorcinarenes or oligophenylenes demonstrate.

Plan of Presentation

In this thesis, the elucidation of the mechanism by which the tetraarylboronic acid resorcinarenes interact with sugar molecules and promote a change in the solution color is explored. Another facet of our macrocycle research, which utilizes resorcinarenes as scaffolds for robust, shape-persistent tubular materials, is then presented. To this end, the synthesis of resorcinarenes containing four appended oligophenylene rods (hereafter referred to as resorcinarene-oligophenylene compounds) is detailed. The synthesis and characterization of these tubular compounds represents the primary focus of this work.

The author's role, in a group effort to determine the mechanism by which the unmodified resorcinarenes (in this case, the structurally simpler tetramethyl-substituted resorcinarenes) aid in the colorimetric detection and quantification of sugar and sugar phosphate analytes, is described in Chapter 2. Upon heating a dimethyl sulfoxide

(DMSO) solution of the resorcinarene, the macrocycle oxidatively decomposes to form highly chromophoric intermediates (possibly including xanthene dye molecules) that interact with the analyte molecules to produce a drastic, visually discernable color change in solution. Since the intermediates responsible for this change of color are produced in very low yields, the preparation of control standards of key intermediates for comparison to the real system was necessary and was the principle contribution of this author. Thus, further background on the mechanism of this color change and the synthesis of two model intermediate compounds are discussed in Chapter 2.

In Chapter 3, the extension of the lower rim conjugation of the resorcinarene macrocycle by the fourfold addition of various length oligo(*p*-phenylene) rods (hereafter referred to as oligophenylenes) is described. An example of an oligo(*p*-phenylene) rod is shown in Fig. 1.2 for future reference. The characteristics of oligophenylenes and the features that these rods add to the resorcinarenes are discussed, since such an alteration should have an effect on the properties of the parent macrocycle. Moreover, given that the addition of oligophenylene rods of increasing lengths generates a progressively longer aromatic hydrophobic cavity, the properties and applications of tubular molecules are reviewed.

Chapter 3 continues by presenting the synthesis of the resorcinarene-oligophenylene compounds, which is the primary focus of this work. Initially, the preparation of oligophenylene rods containing 2, 4, and 8 phenyl units, employing an iterative molecular doubling approach and Suzuki couplings, is detailed. Next, two methods for incorporating the rods into resorcinarene-oligophenylene compounds are contrasted. Finally, the addition of an aldehyde moiety to oligophenylenes of each

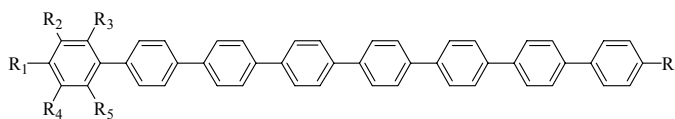


Fig. 1.2. Structure of an octameric oligo(*p*-phenylene) rod. A variety of end groups (R_1 and R_6 including halogen, boronic acid and esters, amines, and amides) side chains(R_2 , R_3 , R_4 , R_5 including carboxylates and ethers) can be employed.

length, followed by the condensation of these modified rods with resorcinol using a Lewis acid catalyst to generate resorcinarene-oligophenylene compounds, is discussed.

The overall goal of this work was to exploit the properties of resorcinarene macrocycles for a variety of biologically significant applications. Through a better understanding of the process leading to the facilitation of the detection and quantification of sugars, sugar phosphates, and other metabolically important biomolecules by our resorcinarenes, future projects could include the design sensors with improved selectivity for specific saccharide analytes. Meanwhile, via the addition of four oligophenylene rods and, consequently, the extension of the conjugation of the lower rim of the resorcinarenes, we intend to address a further goal of synthesizing covalently bonded tubular materials with a fixed cavity diameter. These fixed cavity materials could have potential uses as artificial ion channels and molecular hosts for large guests.

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Chapter 2. Mechanism of Sugar Sensing

Introduction

Sugars and sugar derivatives participate in many metabolic pathways, as mentioned in Chapter 1. Since saccharides play very important roles in biological processes, assays to determine the identity and concentration of sugars in biological samples, such as blood and urine, are of great utility and importance. The lack of a chromophoric moiety in sugar molecules; however, necessitates that sugars and saccharides be detected indirectly. Given that previous non-enzymatic methods for the detection of sugars often use harsh conditions and/or corrosive reagents, the design of artificial sensors for sugars, which do not employ such harsh media, has recently been the focus of much attention.

One subgroup of synthetic sugar sensors incorporates boronic acids.¹ Kuivila et al. observed the ability of boronic acids to solubilize saccharides and other polyalcohols in 1954 and suggested that the behavior was due to the formation of cyclic boronic esters.² Five years later, Lorand and Edwards quantitatively measured the selectivity of phenylboronic acid for various sugars.³ As work progressed in this area, researchers agreed that boronic acids form reversible covalent bonds with 1,2- and 1,3-diols to generate five- and six-membered cyclic esters in nonaqueous or basic aqueous media.^{4,5} (Examples of ester formation under these conditions with phenylboronic acid are shown in Figure 2.1.) Thus, the incorporation of chromophoric moieties into boronic acid based sugar sensors, which allows for the indirect detection of the saccharide, has been a research goal of several researchers, such as Shinkai^{1,6,7} and Anslyn,⁸ since the early 1990s.

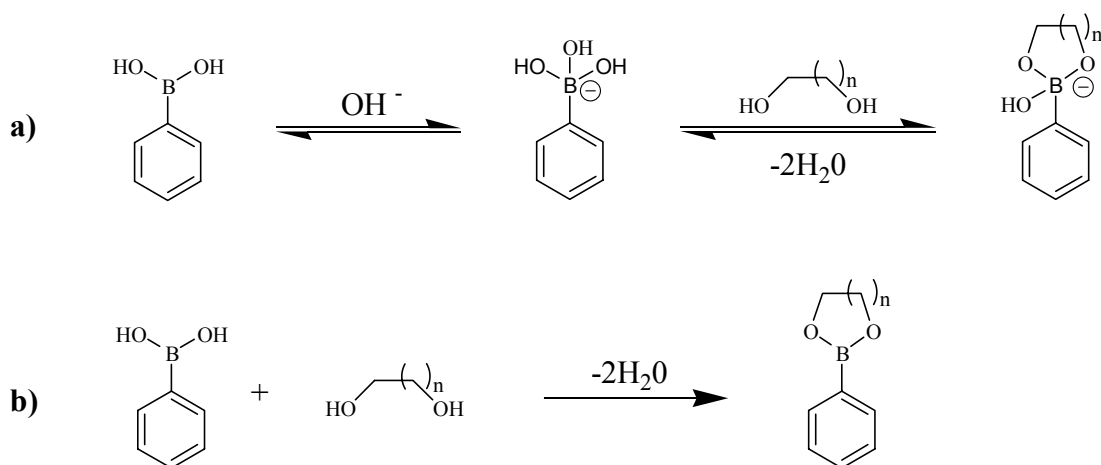
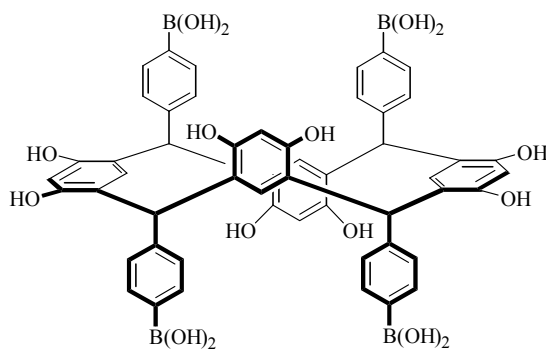


Fig. 2.1. Cyclic boronate ester formation under (a) basic aqueous conditions and (b) aprotic conditions. $n=1,2$. Modified from Ref. 1.

Our research group has developed a sugar sensor which incorporates four boronic acids appended to a resorcinarene macrocycle^{9,10,11} (cf. Fig. 2.2). Heating a colorless solution of **2.1** (5.2 mM in 9:1 DMSO:H₂O) with three equivalents of the saccharides sucrose, D-(-)-fructose, or α -D-glucose at 90°C for 1 minute produces solution colors characteristic of the individual sugar.¹⁰ When these experiments are performed in the



2.1

Fig. 2.2. Compound **2.1**, the C_{2h} (rectt) isomer of the tetraarylboronic acid resorcinarene.

presence of excess Na_2SO_4 , the visual color changes for glucose and fructose become more striking, resulting in a peach and a yellow colored solution, respectively. Since excess Na_2SO_4 is known to promote boronate ester formation under these conditions,⁹ this experiment shows that the boronic acids play a role in promoting a solution color change. Saccharide concentration can be determined by correlating the UV-Visible absorbance at 536 nm (the λ_{max} of the resorcinarene alone) to a standard Beer's law plot for an individual sugar. Similar distinctive solution color changes were observed with **2.1** when sugar acids such as sialic acid and several sugar phosphates were subjected to the same reaction conditions.¹⁰ Since unheated solutions of the resorcinarene macrocycle **2.1** have no visible color, our attention focused on the exact mechanism of the color change.

As part of our mechanistic studies, an investigation into variables which either promoted, suppressed, or did not effect the color change was undertaken. The presence of oxygen caused visible color changes in heated solutions of **2.1** without sugars, and more pronounced color changes when sugars were used under similar conditions,¹⁰ leading to a desire to better understand the exact role of oxygen in the color change mechanism. One possibility for the oxygen dependence was that oxidation of the resorcinol moieties in the macrocycle, followed by loss of water, could result in the formation of xanthene moieties in the macrocycle. Since the early 1900s, xanthenes (cf. Fig. 2.3), especially the flouresceins (where $\text{R}_1=\text{Br}$ or H , $\text{R}_2=\text{H}$, Br , or NO_2 , and $\text{R}_3=o\text{-carboxylatephenyl}$), have been synthesized and used as dyes in a variety of histological applications.^{12,13,14,15} Xanthenes in solution are known to exhibit an array of vibrant colors depending on the other moieties present in the molecule. Consequently, the

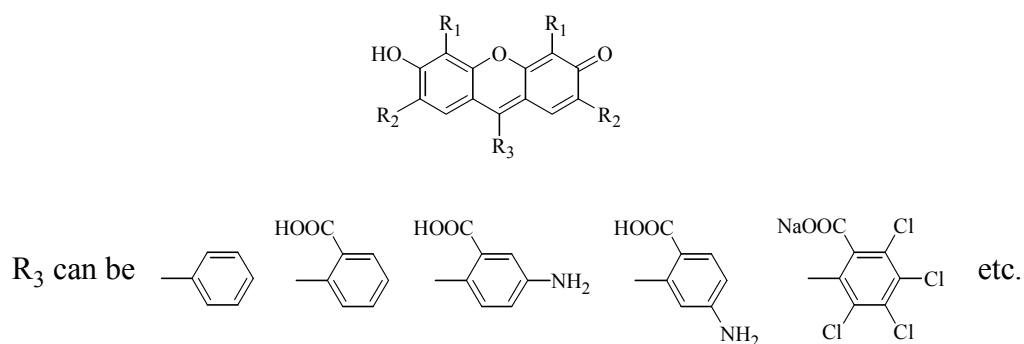
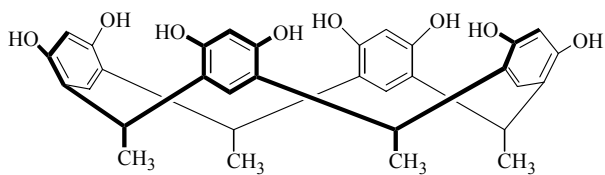


Fig. 2.3. General structure of a xanthene dye. R_1 can be H, Br, or I. R_2 can be H, Br, I, NO_2 , or OH.

formation of xanthenes from heating **2.1**, and the subsequent interaction of these xanthenes with the sugar analytes, appeared to be a plausible explanation for the observed color changes.

In order to test this initial hypothesis (i.e. that the resorcinol units of the macrocycle were forming xanthenes), we decided to select a simpler resorcinarene (cf. Fig. 2.4). Heating a colorless solution of **2.2**, which was previously synthesized and studied for other purposes,¹⁶ with 3.0 equivalents of D-(-)-fructose, α -D-glucose, sucrose, or glucose phosphates also results in characteristic colors for each analyte.¹¹ When visually inspected, however, the colors obtained by heating **2.2** with the various sugars appear paler and less distinct in comparison to the solution colors achieved when using **2.1**. Nonetheless, since **2.2** showed sugar selectivity, and represented a macrocycle with less variables (i.e., the lack of boronic acids), **2.2** was selected to probe the sugar sensing mechanism.

When studying the potential formation of xanthene moieties in the macrocycle **2.2** by oxidation, a key concern was whether the introduction of a xanthene into a macrocycle with only 4 phenyl units results in too much steric strain. Additionally, if



2.2

Fig. 2.4. Compound **2.2**, the C_{4v} (rccc) isomer of the tetramethyl resorcinarene.

the incorporation of a xanthene into **2.2** led to a sterically strained molecule, the macrocycle might open into an acyclic compound and fragment. Xanthenes have been introduced into calix[n]arenes¹⁷ (where n is the number of phenyl rings) with as few as 5 and 6 phenyl units through the dehydration of two vicinal phenol moieties (Fig. 2.5 presents a sample structure of a calixarene and a xanthenocalixarene). However, calix[4]arenes containing xanthenes have never been reported. Initial attempts at the oxidation of **2.2** gave a plethora of products. Two of these products were suitable for single crystal X-ray analysis^{18,19} and lent credence to the concern that the macrocycle might be fragmenting. Formation of the rect structural isomer of **2.2**, also known as the diamond isomer (c.f. Fig. 2.6), was the first indication that bond breaking was

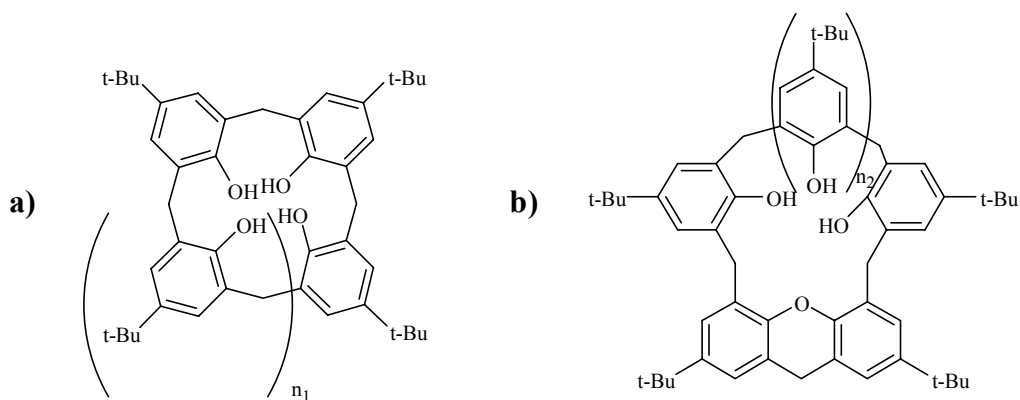


Fig. 2.5. Structures of (a) a sample calixarene and (b) a sample xanthenocalixarene. $n_1=1,2,3$. $n_2=1,2$. Modified from Ref. 17.

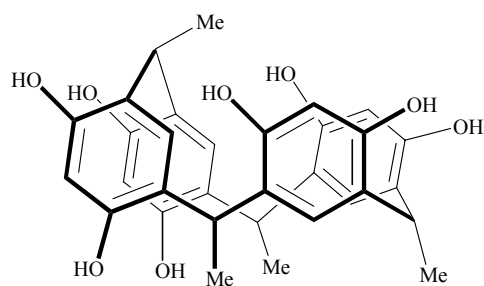


Fig. 2.6. Structure of the rcct isomer of **2.2**.

occurring.¹⁸ Additionally, the isolation of X-ray quality crystals of trimethylsulfonium methanesulfonate indicated that peroxide formation was leading to the decomposition of DMSO.¹⁹ These two phenomena taken together led to the belief that **2.2** was oxidatively fragmenting through a radical pathway.

Since oxidation of **2.2** appeared to be causing bond breaking and possibly fragmentation, the synthesis of fragment model compounds, and the search for these fragments as products of the oxidation of **2.2** was undertaken. Compound **2.3** represents a nonoxidized fragment of **2.2** (cf. Fig. 2.7). While **2.3** has been studied previously,¹⁵ to the best of our knowledge this compound was never isolated and fully characterized. The xanthene **2.4** (cf. Fig. 2.7) embodies an oxidized fragment of **2.2** and a potential chromophore. Compound **2.4** was synthesized originally in 1923 by Sen and Sarkar.^{13,14} However, since many key characterization techniques were unavailable at that time, a full spectral characterization was performed in this study. Furthermore, while **2.4** is commercially available from Aldrich, purity is not guaranteed. Upon analysis, the commercial sample obtained was a mixture of two products, which proved difficult to separate. Thus, a fresh sample of **2.4** was synthesized using the Sen and Sarkar method,^{13,14} and then this sample was subjected to full characterization. The

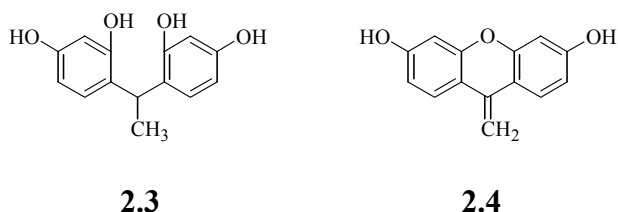


Fig. 2.7. Compounds **2.3** and **2.4**.

characterization of the fresh sample of **2.4** was subsequently used for comparison with the data from the oxidation of **2.2**.

In the rest of this chapter, a description of the characterization of fragments resulting from the oxidation of **2.2** in DMSO is presented. As part of this effort, the synthesis and spectral data for the model fragments **2.3** and **2.4** are discussed. The search for **2.3** and **2.4** amongst the products of the oxidation of the macrocycle **2.2** is also described. Through the preparative scale HPLC isolation of fractions from a crude reaction mixture of oxidized **2.2**, and the search for the characteristic signals of **2.3** and **2.4** in the proton NMR and MALDI-MS of the isolated fraction, compounds **2.3** and **2.4** are established as products of the oxidation of **2.2**. Finally, since the fragmentation and oxidation of the resorcinarene **2.2** has been confirmed in this research, further studies of the color change mechanism are proposed.

Experimental

Materials and methods

For all compounds that were purchased, vendor and purity information is available in Appendix 1. All chemicals were utilized without further purification. Unless otherwise stated, all non-aqueous reactions were carried out in an oxygen free, dry nitrogen atmosphere and in oven-dried glassware. Analytical thin-layer chromatography (TLC) was performed using general purpose 250- μ m silica gel on glass (Scientific

Adsorbents Inc.). Flash chromatography columns were prepared with silica gel (Scientific Adsorbents Inc., 32-63 μm particle size, 60 Å pore size). Proton and carbon NMR spectra were obtained with a Bruker AC-250 spectrometer, a Bruker AC-400 spectrometer, or a Bruker AC-500. Mass spectra were acquired using a Bruker Proflex III MALDI Mass Spectrometer.

Characterization data for compounds **2.3** and **2.4** is shown in the Discussion section of this chapter. The proton NMR spectra for these compounds are also presented in the discussion section of this chapter.

Synthesis

Compound 2.3: Acetaldehyde (0.51 mL, 9.08 mmol) was added to a 0°C solution of resorcinol (2.0 g, 18.1 mmol) in EtOH (30 mL) under a nitrogen atmosphere. Concentrated HCl (15 mL) was then added dropwise to the cooled solution. The reaction was stirred for 24 hours after warming to room temperature for several hours. The reaction mixture was neutralized with a saturated aqueous solution of sodium bicarbonate and then reacidified to pH 5 with concentrated HCl. The EtOH was removed under reduced pressure, and the remaining water solution was extracted with EtOAc (3 x 100 mL). The organic layers were combined, dried with MgSO_4 , and concentrated under reduced pressure to yield 2.46 g crude reaction mixture. Separation by flash chromatography (gradient of 7.5% MeOH:92.5% DCM until the unreacted resorcinol eluted, then 10% MeOH:90% DCM thereafter) yielded 0.325 g (14.5%) of compound **2.3**.

Compound 2.4: Compound **2.4** was prepared by the method published by Sen and Sarkar.^{13,14} Briefly, a mixture of resorcinol (2.2 g, 20 mmol) and 2',4'-

dihydroxyacetophenone (3.04 g, 20 mmol) was heated in the presence of anhydrous zinc chloride (1.0 g, 7.3 mmol) at 140°C for 3 hours. Upon cooling, the solid product was washed with hot water and acidified with hydrochloric acid. The resulting precipitate was purified by recrystallization with ethanol to yield 0.159 g (3.51%) of compound **2.4**

Discussion

As mentioned in the Introduction, the main focus of this chapter is the elucidation of the mechanism by which our resorcinarene macrocycles colorimetrically sense saccharides, sugar phosphates, and sugar acids in solution. In furtherance of this goal, this discussion presents the synthesis and characterization of fragment model compounds **2.3** and **2.4** and the search for these compounds amongst the products of the oxidation of **2.2** in DMSO solution.

Synthesis of **2.3** was accomplished through the acid-catalyzed condensation of two equivalents of resorcinol with one equivalent of acetaldehyde (cf. Fig. 2.8). This reaction led to several products including unreacted resorcinol, **2.3**, and the macrocycle **2.2**; however, compound **2.3** was successfully isolated in 14.5% yield using flash chromatography. Compound **2.3** was then subjected to full characterization (cf. Table 2.1 for characterization data and Figs. 2.9 and 2.10 for the proton NMR spectrum of **2.3** in MeOH-d₄).

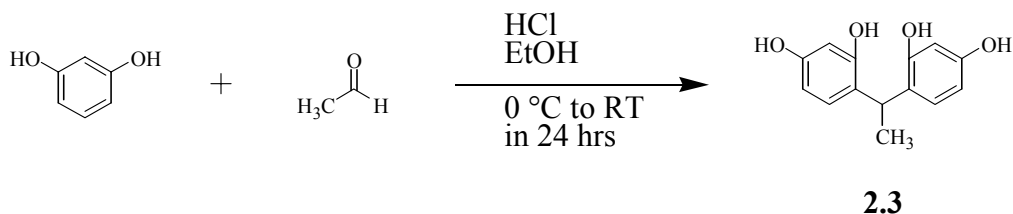


Fig. 2.8. Synthesis of compound **2.3**

In a similar fashion, compound **2.4** was prepared by the known zinc chloride-catalyzed condensation of resorcinol and 2',4'-dihydroxyaceophenone followed by dehydration^{13,14} (cf. Fig. 2.11). Purification by recrystallization resulted in a 3.51% yield of **2.4**. Since key characterization techniques had not been developed at the time **2.4** was originally synthesized,^{13,14} a full spectral characterization of the compound was performed. The data acquired during this characterization is presented in Table 2.2, and Figs. 2.12 and 2.13 show for the proton NMR spectrum of **2.4** in MeOH-d₄.

With the successful synthesis of the model fragment compounds (cf. Section B), the search for **2.3** and **2.4** as products of the oxidation of **2.2** in DMSO was undertaken.

Table 2.1. Characterization data for compound **2.3**.

Technique	Conditions	Data
TLC	10 % MeOH:90 % DCM mobile phase	R _f =0.26
HPLC	Gradient 50 % MeOH:50 % H ₂ O to 100% MeOH in 20 minutes then 100% MeOH for 30 minutes thereafter, 5 mL min, λ=255 nm, Dynamax 60Å C ₁₈ 21.4 mm x 25 cm	Retention time=18 min
Melting point		206-207 °C
¹ H NMR	250 MHz Solvent = MeOH-d ₄	δ 1.46 (d, ³ J = 7.3 Hz, 3 H), 4.53 (q, ³ J = 7.3 Hz, 1 H), 6.18-6.22 (m, overlap of d and dd, 4 H), 6.89 (d, ³ J = 8.0 Hz, 2 H)
¹³ C NMR	62.9 MHz Solvent = MeOH-d ₄	δ 20.5, 30.5, 103.5, 107.6, 125.6, 128.8, 156.0, 157.0
¹ H NMR	250 MHz Solvent = DMSO-d ₆	δ 1.25 (d, ³ J = 7.2 Hz, 3H), 4.36 (q, ³ J = 7.2 Hz, 1 H), 6.04 (dd, ³ J = 8.3 Hz, ⁴ J = 2.4 Hz, 2 H), 6.16 (d, ⁴ J = 2.4 Hz, 2H), 6.66 (d, ³ J = 8.3 Hz, 2 H), 8.85 (bs, 4H)
MALDI-MS	Matrix = Dithranol	246.1 obs. (M-H), (246.09 calc'd)

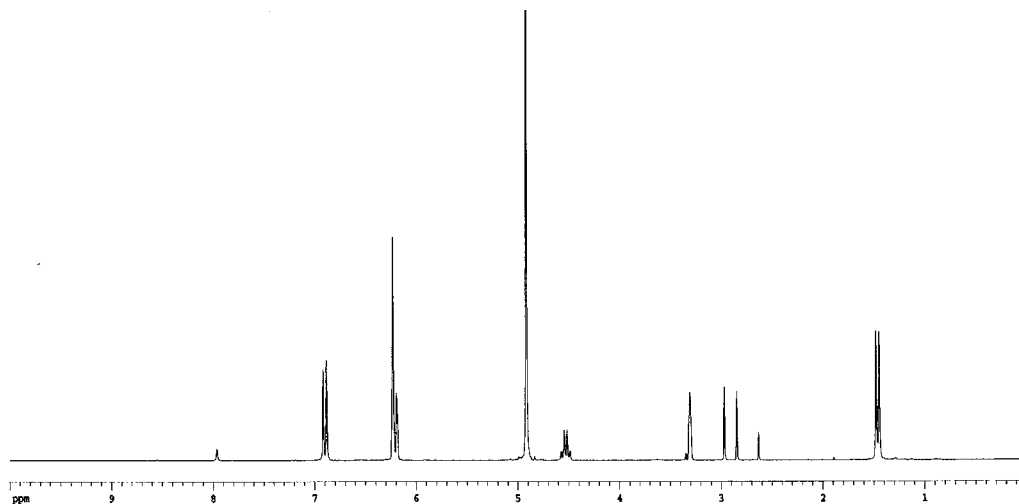


Fig. 2.9. Proton NMR spectrum of **2.3**. Solvent is MeOH- d_4 .

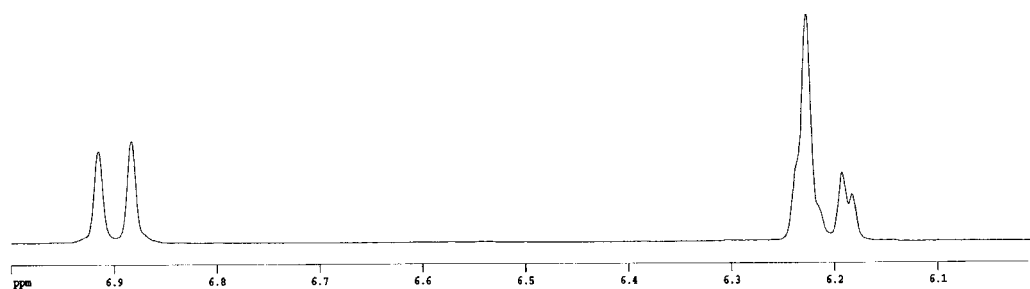


Fig. 2.10. Enlargement of the aromatic region of the proton NMR spectrum of **2.3**. Solvent is MeOH- d_4 .

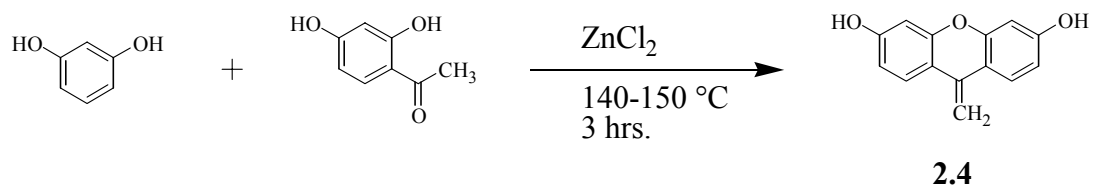


Fig. 2.11. Synthesis of compound **2.4**.

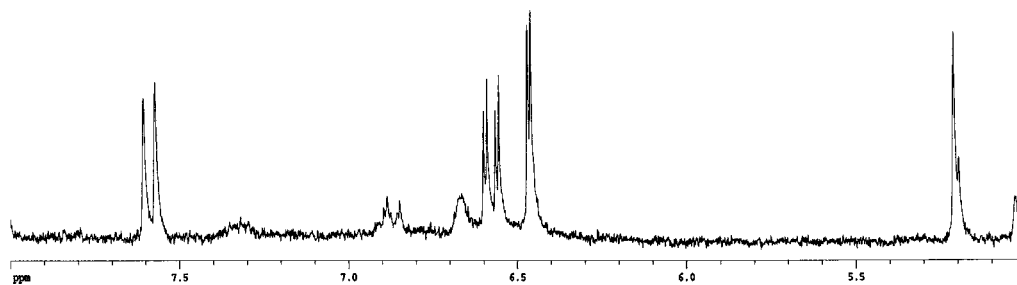


Fig. 2.13. Enlargement of the aromatic region of the proton NMR spectrum of **2.4**. Solvent is MeOH- d_4 .

DMSO was removed *in vacuo*, the residual solid was dissolved in methanol and subjected to HPLC analysis using the same conditions as the analysis of **2.3** and **2.4** (cf. Tables 2.1 and 2.2). The chromatograph indicated a large number of products including peaks near the known retention times of compounds **2.3** and **2.4** (c.f. Fig. 2.14) as well as some remaining **2.2** at 31 minutes. As part of an effort to find **2.3** (retention time = 18 minutes) and **2.4** (retention time = 23.3 minutes) in this reaction mixture, a preparative scale HPLC isolation of two fractions with retention times of 18-20 minutes (Isolate A) and 21-24 minutes (Isolate B), respectively, was performed.

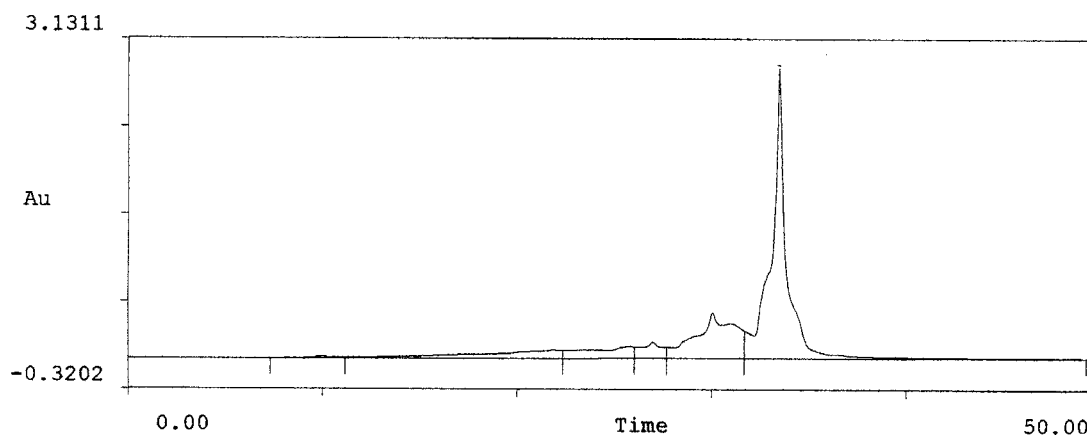


Fig. 2.14. HPLC trace of the crude reaction mixture of the oxidation of **2.2**. Time is shown in minutes.

The MALDI mass spectrum (with a dithranol matrix) of Isolate A gave a peak at 247.8, which confirms the presence of **2.3** as one of the various products in this fraction. In addition, key resonances from the proton NMR of **2.3** in MeOH- d_4 were found in the proton NMR (500 MHz) of Isolate A when taken in the same solvent. Table 2.3 catalogues the corresponding peaks in each spectrum, while Figs. 2.15 and 2.16 display the proton NMR spectrum (500 MHz) of Isolate A. Although several products are present in Isolate A, the spectral evidence clearly supports the existence of **2.3** in this fraction. In turn, having established that **2.3** is in Isolate A, we have also shown that **2.3** is a product of the oxidation of **2.2** in DMSO. Therefore, the macrocycle **2.2** fragments upon oxidation.

The second HPLC isolate (21-24 minutes), or Isolate B, did not lead to such successful results. While a peak at 225.87 in the MALDI mass spectrum (with an anthracene matrix) corresponded to the calculated mass of 226.06 for **2.4**, the proton NMR spectra (500 MHz) of Isolate B did not appear to contain the key resonances for the xanthene **2.4**. One possible explanation for this disparity could be that **2.4** is present in

Table 2.3. A resonance by resonance comparison of the NMR spectra of compound **2.3** and Isolate A (i.e., the 18-20 minute HPLC isolate from a crude oxidized reaction mixture of **2.2**). (Solvent = MeOH- d_4).

Compound 2.3 (250 MHz)	Crude oxidized reaction mixture of 2.2 (18-20 minute HPLC isolate) (500 MHz)
1.46 (d, $^3J = 7.3$ Hz) Peaks at 1.44 and 1.47 ppm	1.48 (d, $^3J = 7.3$ Hz) Peaks at 1.47 and 1.48 ppm
4.53 (q, $^3J = 7.3$ Hz) Peaks at 4.48, 4.51, 4.54, and 4.57 ppm	Peaks at 4.49, 4.51, and 4.53 Among several other peaks
6.18-6.22 (m, overlap of d and dd) Peaks at 6.18, 6.19, and 6.22 ppm	Same peak pattern Peaks at 6.21, 6.23, and 6.24 ppm
6.89 (d, $^3J = 8.0$ Hz) Peaks at 6.88 and 6.91 ppm	6.89 (d, $^3J = 8.2$ Hz) Peaks at 6.88 and 6.90 ppm

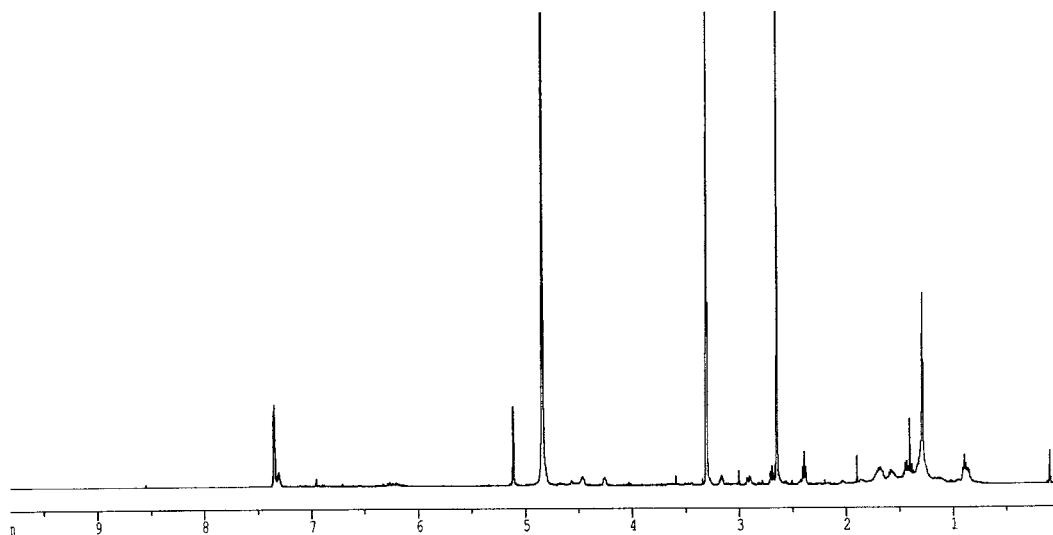


Fig. 2.15. Proton NMR spectrum of Isolate A (i.e., the 18-20 minute isolate). Solvent is MeOH- d_4 .

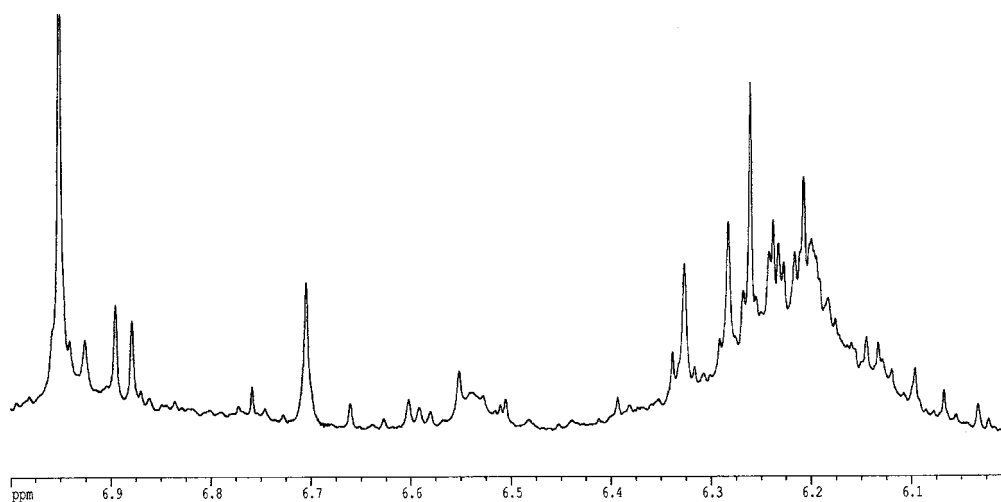


Fig. 2.16. Enlargement of the aromatic region of the proton NMR spectrum of Isolate A (i.e., the 18-20 minute isolate). Solvent is MeOH- d_4 .

Isolate B at very low concentrations and, therefore, is undetectable by NMR. Continued work in establishing that **2.4** is a product of the oxidation of the macrocycle **2.2** in DMSO is currently underway in our research group.

Conclusions

One of the primary areas of research in the Strongin research group is the synthesis of artificial sensors for sugars, sugar phosphates, and sugar acids. An important part of this work is the elucidation of the mechanism by which our resorcinarene macrocycles allow for the identification and quantitation of saccharides and their derivatives in solution. Initial studies have led to the idea that, in the presence of oxygen, the macrocycles fragment and oxidize via a radical pathway to form a chromophoric species that, subsequently, could then interact with the sugar analytes.

In an effort to ascertain if this fragmentation and oxidation was occurring, the macrocycle **2.2** (c.f. Fig. 2.2) was chosen for the current research. Compounds **2.3** and **2.4** (c.f. Fig.2.7), which represent potential fragments of **2.2**, were then synthesized and characterized. Knowing the characteristics of these fragments, the search for **2.3** and **2.4** amongst the products of an oxidation of **2.2** was undertaken. The presence of **2.3** was confirmed in a crude reaction mixture of oxidized **2.2** by MALDI-MS and proton NMR; however, only mass spectral evidence of **2.4** was found in the same crude reaction mixture. Further efforts to establish **2.4** as a product of the oxidation of **2.2** are underway.

Nonetheless, the proof of macrocycle fragmentation has led to the proposal of a mechanism for this phenomena, which is shown in Figure 2.17. The reaction starts when the macrocycle abstracts a radical from oxygen in the air. (Oxygen radicals generated in this step further reacts to form peroxides that, in turn, react with DMSO to form the trimethylsulfonium methanesulfonate seen as a product in our initial studies.)

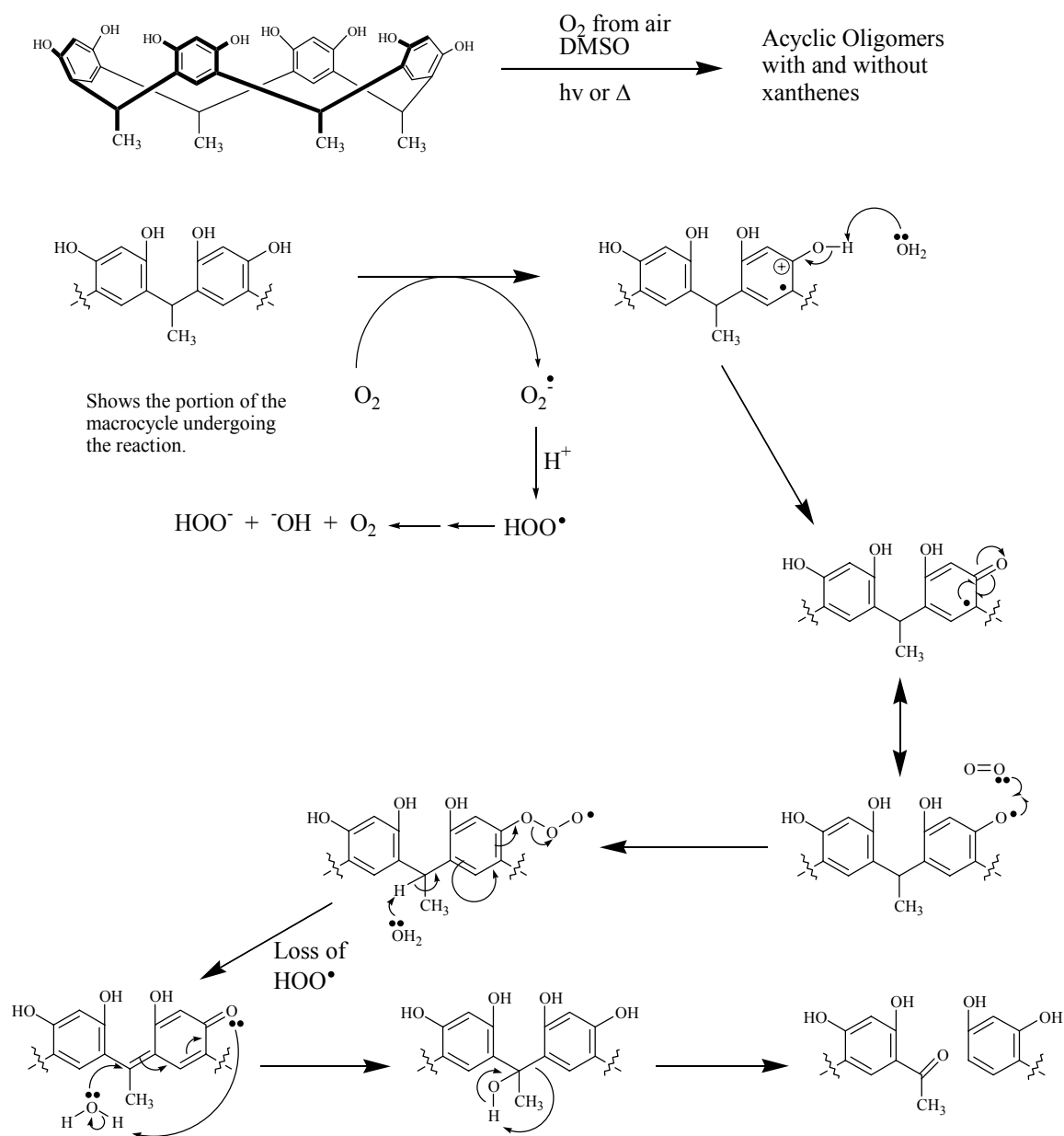


Fig. 2.17. Mechanism of the oxidative fragmentation of the resorcinarene macrocycles.

The proton on the hydroxyl group adjacent to the radical cation in the macrocycle can be removed by residual water in the DMSO leading to a species vulnerable to attack by molecular oxygen. With the addition of a molecule of oxygen, a bridging proton can be abstracted by a water molecule. Simultaneous to this proton loss, a peroxide radical is

liberated. This results in a highly strained species which then fragments to produce acyclic species. These acyclic species continue to oxidatively fragment to generate the variety of products that are seen in the oxidation of **2.2**.

Future work in the mechanistic portion of the sugar-sensing project includes establishing that xanthenes are also products of the oxidation of the resorcinarenes in DMSO solution. Once the xanthene chromophores have been isolated, the mechanism of the solution color change will need to be fully elucidated. Part of this effort will be the determination of the exact nature of the interaction of the xanthenes with saccharides analytes.

The next chapter presents another facet of our macrocycle research, namely the synthesis of modified resorcinarenes with potential applications as tubular materials.

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Chapter 3. Incorporation of Resorcinarenes into Tubular Materials

Introduction

Tubular materials have recently been the focus of much attention, due to an abundance of proposed applications. Naturally occurring tubular molecules are known to function in antigen and secondary metabolite recognition,^{1,2,3} biomembrane transport,⁴ and catalysis.^{3,5} Additionally, unnatural fullerene nanotubes are high-strength materials which can act as either metals or semiconductors, depending on the symmetry of the structure.⁶ In this research group, the use of resorcinarene macrocycles as scaffolds for the controlled synthesis of oligoaromatic tubular materials is an extension of our work with resorcinarenes as sugar sensors (i.e. Chapter 2). Therefore, a description of the motivation, design, and synthesis of a robust, shape-persistent tubular molecule that incorporates both a resorcinarene and four oligophenylene rods is presented in this chapter.

Since the first synthesis of resorcinarene macrocycles was published in 1872,^{7,8} many applications for these molecules have been proposed (cf. Chapter 1). The work presented in this chapter will address primarily the use of resorcinarenes in host-guest chemistry,^{9,10} drug delivery,¹¹ and artificial ion channels.¹² Resorcinarenes are of particular interest in these applications, since these molecules possess a cavity diameter of 7 Å¹³ (the same as the diameter of fullerene[60] and the smallest fullerene nanotubes) which, in turn, implies that tubular molecules incorporating resorcinarenes could allow the binding and transport of guest molecules.

One method for enhancing the properties of resorcinarenes, especially the selectivity, is to functionalize the lower rim¹⁰ (which is derived from the aldehyde). Of

specific interest to us is the extension of the conjugation of this lower rim to generate progressively longer hydrophobic, aromatic cavities. Previously, only one description of such an expansion (which involved a multistep process that incorporated a phenylacetylene moiety) was reported by Cram et al.¹⁴ Lewis and Strongin later performed a direct conjugation extension of the lower rim of a resorcinarene using a fourfold Suzuki coupling,¹⁵ (cf. Fig. 3.1). The focus of this chapter, however, will be on extending the conjugation of the lower rim of the resorcinarene cavity via the addition of various length oligo(*p*-phenylene) rods.

Oligo- and poly(*p*-phenylene)s represent a class of conjugated rigid rods with a wide variety of properties and applications. In addition to being well-known redox and chromophoric materials, oligophenylenes have been used as chain stiffening building blocks in polyimides and aromatic polyesters.¹⁶ Oligophenylenes have also been employed as models for rod-like polyaromatic and liquid crystalline materials.¹⁶ Furthermore, oligophenylene rods have been shown to incorporate into barrel-like folds,¹⁷ ion channels,¹⁸ and amphiphilic materials.¹⁹

The full potential of oligophenylene rods has not been realized, however, as the synthesis, isolation, and purification of these molecules are quite challenging.²⁰

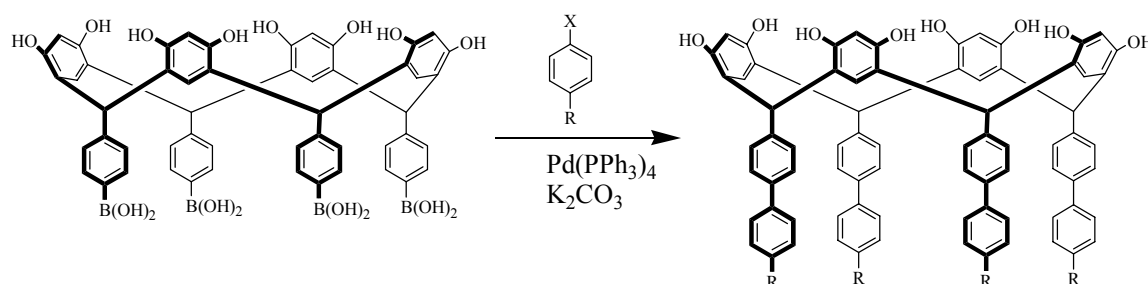


Fig. 3.1. Fourfold Suzuki coupling of phenyl bromides to the lower rim of a tetraarylboronic acid resorcinarene. When X=I and R=H, the reaction gives 26% yield. When X=Br and R=Ph, the reaction gives 11% yield.

Iterative molecular doubling has been successfully employed in the synthesis of relatively long oligo(*p*-phenylene)s.²¹ For example, our group recently reported the synthesis²² of multigram quantities of oligophenylene rods containing 2,4, and 8 phenyl units (cf. Fig. 3.2). While an iterative molecular doubling approach was applied, no preparative scale chromatography or formal protecting groups were used. Instead of boronic acids, which are difficult to isolate, more soluble boronic esters were employed in the Suzuki couplings. Additionally, readily interconvertible carboxylate side groups were included on alternating phenyl rings to allow for versatility in later functionalization. Specific contributions to improve procedures and yields in these reactions are highlighted in the next section.

Through the addition of various length oligophenylene rods to the lower rim of a resorcinarene macrocycle, new materials (resorcinarene-oligophenylene compounds) could be created which would embody the properties and utilities of both the resorcinarenes and the oligo(*p*-phenylene)s. These well-defined, three-dimensional molecules have the potential to act as better artificial ion channels or molecular hosts than resorcinarenes alone. For example, the addition of four octameric oligophenylene rods to the resorcinarene scaffold would result in an elongated aromatic cavity of 37Å (cf. Fig. 3.3). This aromatic cavity is long enough to span the hydrophobic portion of a typical Egg Yolk Phosphatidyl Choline (EYPC) lipid bilayer, while the phenolic –OH groups on the upper rim of the resorcinarene are appropriate for interaction with the hydrophilic portion of the bilayer. A description of the synthesis of molecular channels (representing the fourfold addition of dimeric, tetrameric, and octameric oligophenylene rods to the lower rim of a resorcinarene) is also presented in the following sections.

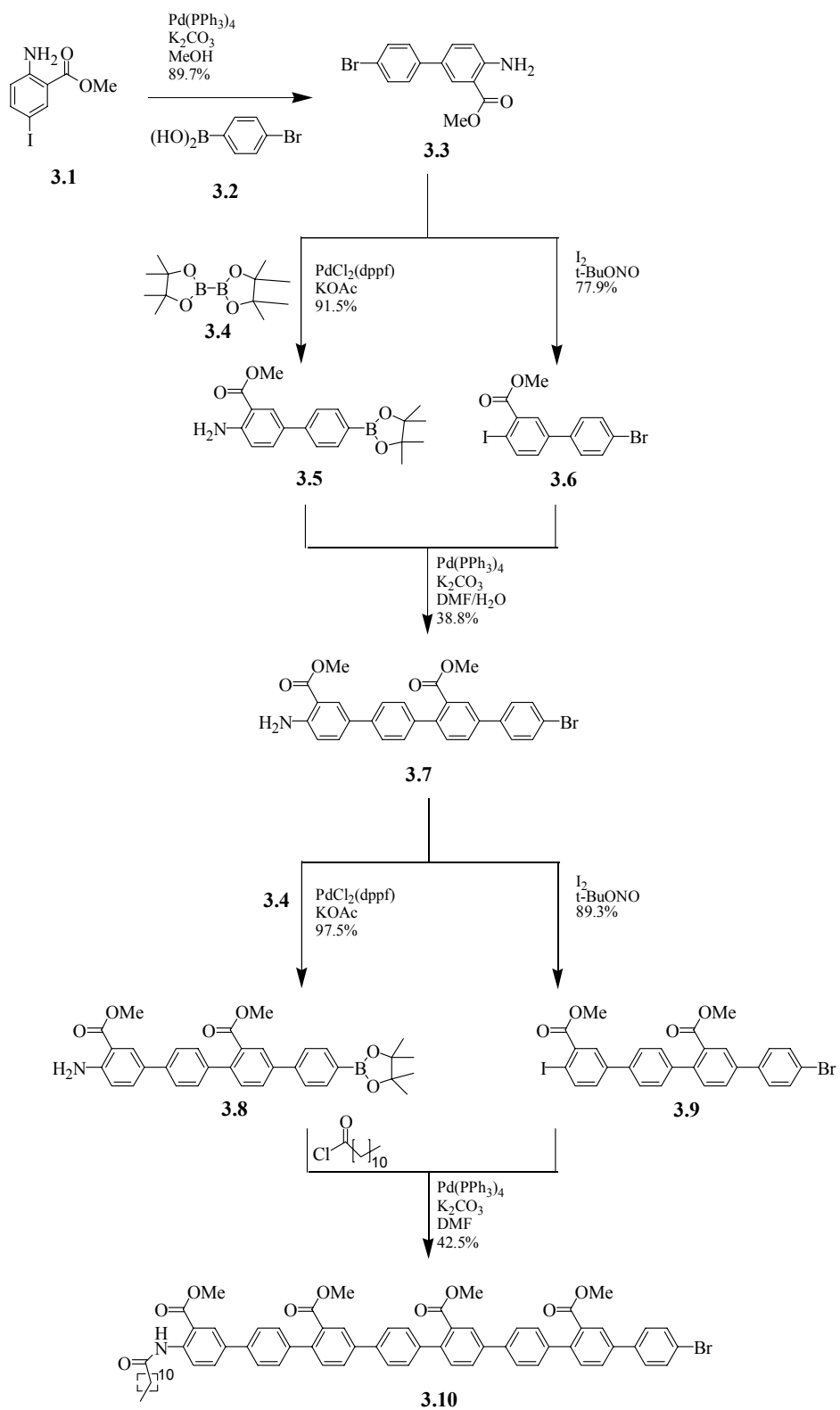


Fig. 3.2. Synthesis of the biphenyl (**3.3**), tetraphenyl (**3.7**), and octaphenyl (**3.10**) compounds.

In addition to possible applications as artificial ion channels, we intend to use the resorcinarene-oligophenylene compounds, synthesized herein, as molecular hosts. The organic phosphates represent one potential group of guests (where guest implies an analyte molecule which is bound by the host and whose concentration may be ascertained by a change in the UV or fluorescence spectra of the total solution). Of particular interest is lysophosphatidic acid (LPA), which is a newly discovered marker in diagnostic tests for the early stages of ovarian cancer.²³ Phosphates are normally difficult to detect, since these molecules contain no visible chromophoric moieties. Recently, we have shown that boronic acid resorcinarenes (without attached oligophenylene rods) bind sugar phosphates in solution.²⁴ The addition of oligophenylene rods to the resorcinarene hosts creates a hydrophobic pocket which could enhance the ability of the resorcinarenes to bind phosphates with long fatty acid tails (such as LPA). We will propose a

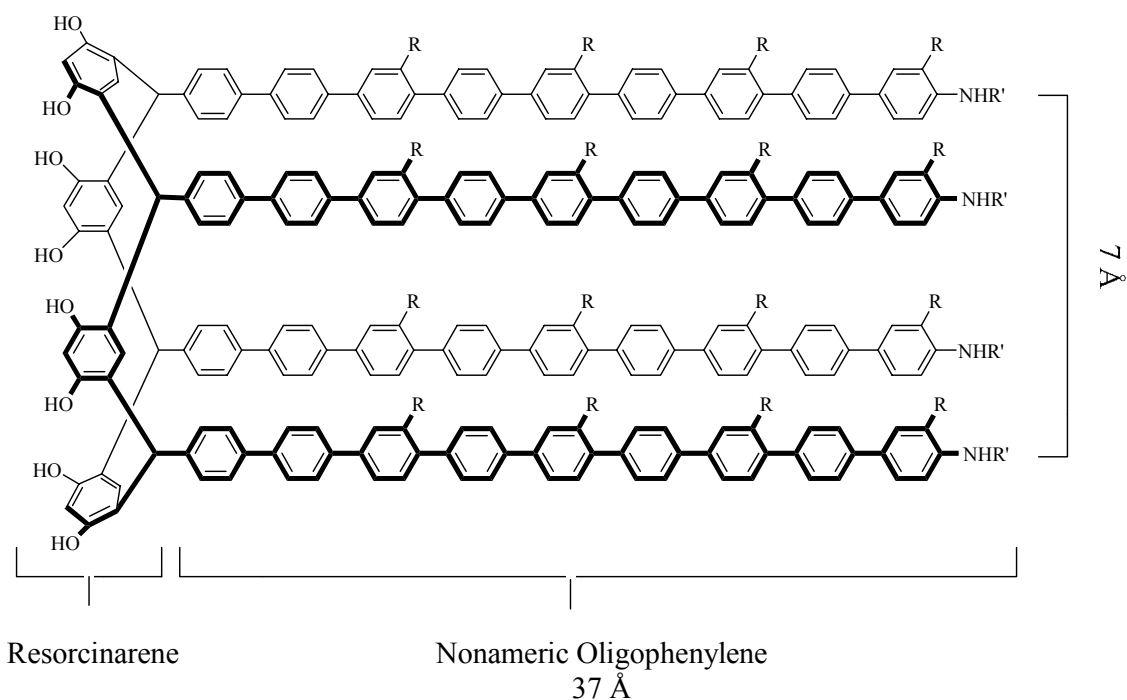


Fig. 3.3. Resorcinarene macrocycle with 4 octameric oligophenylene rods attached to its base. $R=\text{COOMe}$ $R'=\text{CO}(\text{C}_{10}\text{H}_{23})$.

quantitative study of the binding constants of our modified resorcinarene hosts for various phosphate analytes using UV-VIS spectroscopy later in this chapter.

In the rest of this chapter, a description of the synthesis of several three-dimensional, shape-persistent molecules, that incorporate both a resorcinarene macrocycle and four various length oligophenylene rods will be presented. The characterization of these resorcinarene-oligophenylene compounds by proton nuclear magnetic resonance (^1H NMR) and Matrix-Assisted Laser Desorption Ionization Mass Spectra (MALDI-MS) is discussed. These compounds were synthesized with the idea that such new molecules will assimilate the properties of both resorcinarenes and oligophenylenes. Particularly, we are interested in investigating the properties of these new tubular molecules as potential ion channels or molecular sensing hosts.

Experimental

Materials and methods

For all compounds which were purchased, vendor and purity information is available in Appendix 1. Resorcinol was recrystallized in benzene prior to use. Anhydrous DMF was acquired in Sure Seal bottles. All other chemicals were utilized without further purification. Unless otherwise stated, all non-aqueous reactions were carried out in an oxygen free, dry nitrogen atmosphere and in oven-dried glassware. Analytical thin-layer chromatography (TLC) was performed using general purpose 250- μm silica gel on glass (Scientific Adsorbents Inc.). Flash chromatography columns were prepared with silica gel (Scientific Adsorbents Inc., 32-63 μm particle size, 60 Å pore size). Proton NMR spectra were obtained with a Bruker AC-250 spectrometer. Mass spectra were acquired using a Bruker Proflex III MALDI Mass Spectrometer.

Characterization data and proton NMR spectra for compounds **3.15**, **3.16A**, **3.16B**, **3.17A**, and **3.17B** are presented in the Discussion section of this chapter. (Refer to Figs. 3.2, 3.6, 3.10, and 3.15 for the numbering of compounds discussed below.) The synthesis of compounds **3.1**, **3.3**, and **3.5-3.14** were performed by other members of this research group.^{22, 25}

Synthesis

Compound 3.6: T-Butyl nitrite (1.40 mL, 90%, 3.47 mmol) was added to a 0°C solution of **3.3** (1.0g, 3.15 mmol) in benzene (60 mL).²² After 5 minutes, I₂ (0.960g, 3.78 mmol) was also added to the reaction mixture. The reaction was warmed to room temperature overnight and then heated to 60°C for 10 minutes. H₂O (60 mL) was added to the cooled reaction mixture, and the layers separated. The aqueous phase was extracted with DCM (3 x 60 mL). The organic layers were combined and dried with MgSO₄, and the solvent was removed under reduced pressure. The residual was coevaporated with hexanes, triturated with hexanes, and filtered to afford 1.21g (91.6%) of a brown solid.

Compound 3.15: Compound **3.10** (0.0900g, 0.0805 mmol),²² 4-formylbenzeneboronic acid (0.0133g, 0.0885 mmol), K₂CO₃ (0.0222g, 0.161 mmol) and tetrakis(triphenylphosphine) palladium(0) (0.01 g, 3 x 10⁻³ mmol) were dissolved in anhydrous DMF and heated to 80°C overnight. The cooled reaction mixture was filtered through a celite pad, and the solvent was removed from the resulting filtrate *in vacuo*. Both H₂O (100 mL) and DCM (100 mL) were added to the residual, and the aqueous layer was extracted with DCM (3 x 100 mL). The organic layers were combined, dried with MgSO₄, and concentrated under reduced pressure. Flash chromatography (gradient

of 7.5% EtOH:92.5 % DCM to 10% EtOH:90 DCM)) yielded enough sample to get a ^1H NMR spectra.

Compounds 3.16A and 3.16B: Borontrifluoroetherate (0.35 mL, 2.7 mmol) was added to a solution of **3.13** (1.00g, 1.95 mmol) and resorcinol (0.236g, 2.14 mmol) in chloroform (50 mL).²⁵ The reaction was allowed to stir for two days, and then the solvent was removed by coevaporation with EtOH under reduced pressure. Flash chromatography (gradient of 100% DCM to 85% DCM:15% MeOH by 2.5% MeOH increments) on the resultant solid yielded 0.243g (20.6 %) C_{4v} -isomer of compound **16** (i.e., **3.16A**) and 0.642g (54.4 %) C_{2h} -isomer of compound **3.16** (i.e., **3.16B**).

Compound 3.17A and 3.17B: Borontrifluoroetherate (0.0249 mL, 0.195 mmol) was added to a solution of **3.14** (0.100g, 0.138 mmol) and resorcinol (0.0169g, 0.153 mmol) in chloroform (12.5 mL).²⁵ The reaction was allowed to stir for 2 days, and then the solvent was removed by coevaporation with EtOH under reduced pressure. Flash chromatography (gradient of 100% DCM to 85% DCM:15% MeOH 2.5% MeOH increments) on the resultant solid yielded 0.028 g (24.8 %) C_{4v} -isomer of compound **3.17**(i.e., **3.17A**) and 0.080 g (71.1 %) C_{2h} -isomer of compound **3.17** (i.e., **3.17B**). After this separation, the **3.17A** and **3.17B** were still not pure; therefore, further purification will be required.

Discussion

As mentioned in the Introduction section of this chapter, the primary focus of this chapter and this research is the synthesis of shape-persistent tubular molecules that integrate both a resorcinarene scaffold and four oligophenylene rods. To this end, the current discussion concentrates on two specific areas of study, namely, improvements to

the oligophenylene synthesis, and the synthesis and characterization of resorcinarenes with appended oligophenylene rods.

The synthesis and published yields of oligophenylene rods containing 2,4, and 8 phenyl units²² are shown in Fig 3.2. Since these oligophenylene rods are half of the building blocks for the resorcinarene-oligophenylene compounds, the production of multigram quantities of each of the various length rods was necessary for the overall synthesis of the modified resorcinarenes to progress. During these experiments, the yield of compound **3.6** was improved from 77.9% to 91.6% (a 13.7% increase). This elevated yield was primarily due to a change in the order of the addition of reagents (from adding t-butyl nitrite to a 0°C mixture of a benzene solution of **3.3** and iodine, to adding t-butyl nitrite to a 0°C benzene solution of **3.3** followed by the addition of iodine). The alteration of the procedure prevented the formation of a “gum” which, in turn, made the isolation of **3.6** simpler. (No other attempts on yield improvements for the compounds in Fig. 3.2 were successful.)

With the synthesis of the dimeric (**3.3**), tetrameric (**3.7**), and octameric (**3.10**) oligophenylene rods accomplished, the incorporation of the rods into the resorcinarene macrocycle became the primary research goal. The direct, fourfold Suzuki coupling of **3.3** and **3.7**, respectively, to the lower rim of the C_{4v}-isomer of the boronic acid resorcinarene (in the same manner as Lewis and Strongin¹⁹) was attempted unsuccessfully in our group²⁵ (cf. Fig. 3.4). Steric hindrance in the lower rim of the resorcinarene is a probable reason for the failure of this reaction.

Thus, a different approach for the integration of the oligophenylene rods into a modified resorcinarene macrocycle was required. Instead of adding four

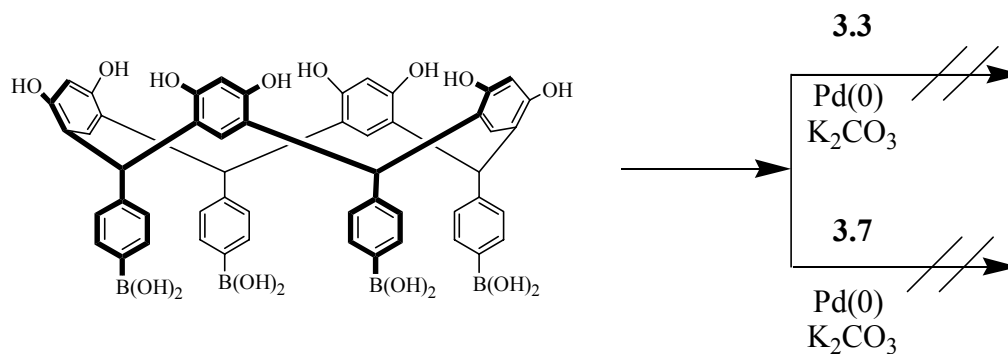


Fig. 3.4. The attempted fourfold Suzuki coupling of **3.3** and **3.7** to the C_{4v} -isomer of a tetraarylboronic acid resorcinarene.

oligophenylene rods directly to the resorcinarene macrocycle, the oligophenylene rods were altered by attaching an aldehyde functional group. These modified rods could, therefore, undergo an acid-catalyzed condensation with resorcinol to form a resorcinarene macrocycle. An aldehyde moiety can be appended to **3.3**, **3.7**, and **3.10** by a Suzuki coupling of the brominated terminus with 4-formylphenylboronic acid. However, since aldehydes and amines can react, the protection of the free amines in **3.3** and **3.7** by amidation was necessary. Lauroyl chloride was selected for this purpose, for the sake of uniformity and to promote the solubility of the products. Therefore, **3.3** was protected with lauroyl chloride in the presence of triethyl amine to give **3.11**, which was then reacted with 4-formylphenylboronic acid in the presence of tetrakis(triphenylphosphine) palladium(0) and potassium carbonate to give **3.12**²⁵ (cf. Fig 3.5). Analogously, **3.7** was converted to the lauroyl amide **3.13**, and the aldehyde **3.14** was synthesized from **3.13**²⁵ (cf. Fig. 3.5). In the case of the octameric oligophenylene rod **3.10** (which was already an amide), a small-scale synthesis of the aldehyde **3.15** from **3.10** was carried out (cf. Fig 3.6) and generated enough sample to perform a proton NMR. Proton NMR data for **3.15** is presented in Table 3.1, while the NMR spectra for this compound is shown in Figs. 3.7 and 3.8.

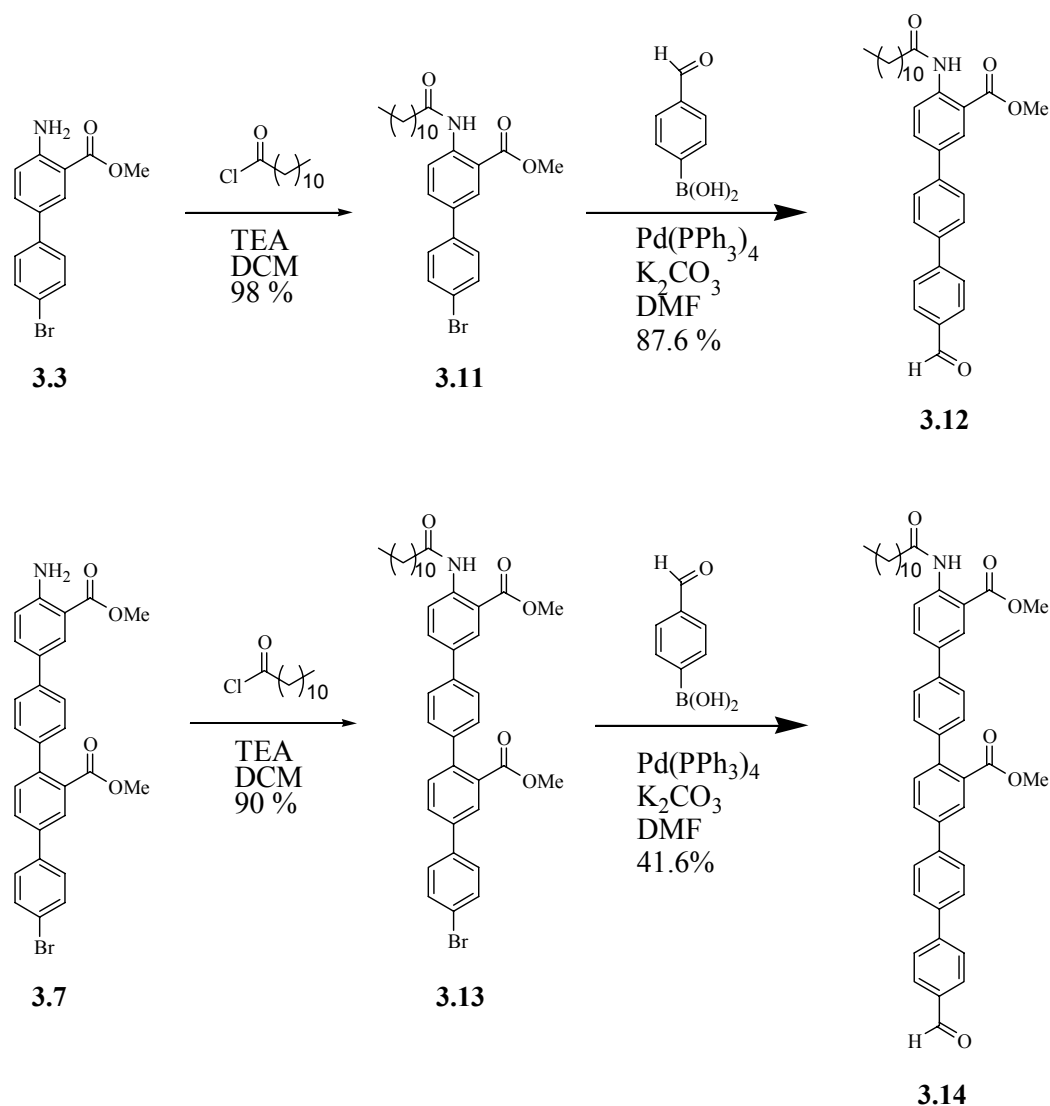


Fig. 3.5. Synthesis of the triphenyl aldehyde (**3.12**) and the pentaphenyl aldehyde (**3.14**).

Once the aldehydes **3.12** and **3.14** had been produced, the acid-catalyzed condensation of these modified oligophenylene rods with resorcinol was attempted. An important consideration in this reaction was the tolerance of the acid used to catalyze the cyclization to the functional groups present in the oligophenylenes. While resorcinarenes are generally made using protic acids, Lewis acids such as trifluoroacetic acid (TFA),²⁶ aluminum trichloride (AlCl_3),²⁷ and boron trifluoride (BF_3)^{27, 28, 29} have been used as milder alternatives in these cyclizations. Thus, we decided to pursue the use of Lewis

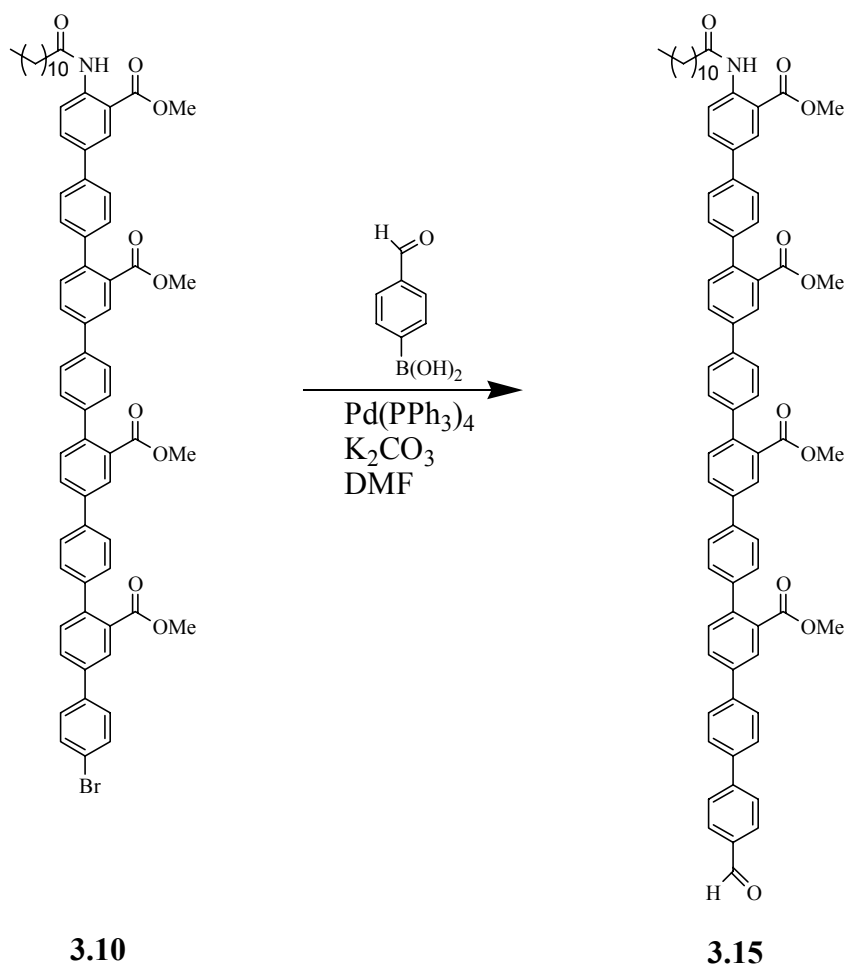


Fig. 3.6. Synthesis of the nonaphenyl aldehyde (**3.15**).

Table 3.1. Characterization Data for compound **3.10**.

Technique	Conditions	Data
^1H NMR	250 MHz Solvent = 10% MeOH- d_4 : 90% CHCl_3 - d_1	δ 0.918 (t, 3 H), 1.30 (m, 15 H), 1.82 (m, 2 H), 2.51 (t, 2 H), 3.78 (bs, 6 H), 4.02 (s, 2 H), 7.48-7.91 (m, 16 H), 8.03 (d, $^3J = 8$ Hz, 1 H), 8.20 (d, $^4J = 2$ Hz, 2H), 8.39 (d, $^4J = 2$ Hz, 1 H), 8.89 (d, $^3J = 9$ Hz, 1 H), 10.12 (s, 1H), 11.11 (s, 1 H)

acids to catalyze the synthesis of the resorcinarene-oligophenylene compounds (cf. Fig. 3.9). As part of this effort, small-scale reactions were attempted to condense **3.12** and

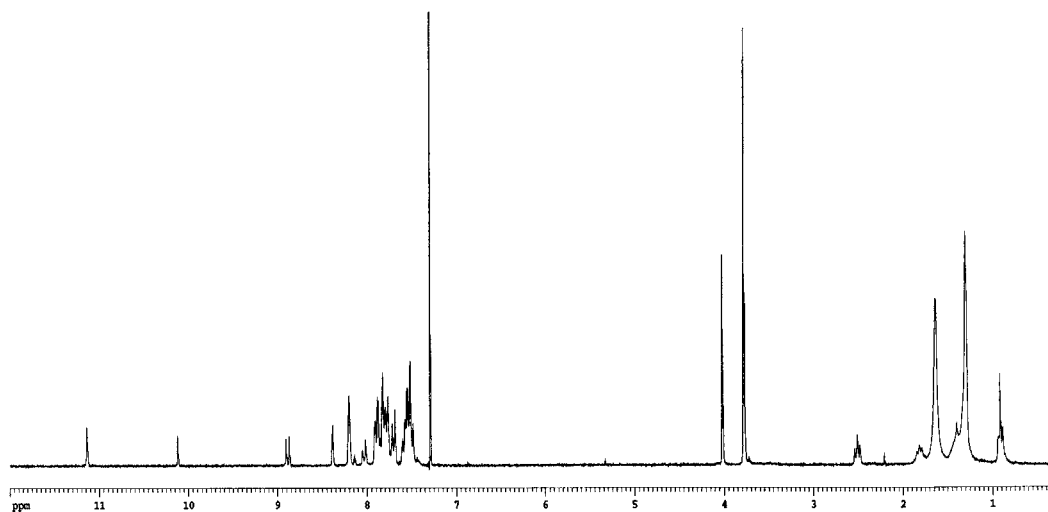


Fig. 3.7. Proton NMR spectrum of **3.15** (250 MHz). Solvent is 10% MeOH- d_4 : 90% $CHCl_3$ - d_1 .

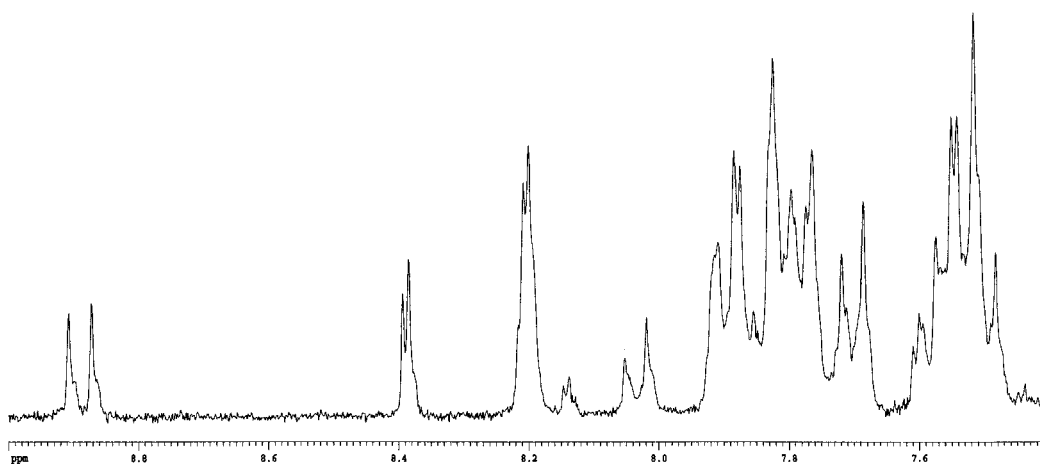


Fig. 3.8. Enlargement of the aromatic region of the proton NMR spectrum of **3.15** (250 MHz). Solvent is 10% MeOH- d_4 :90% $CHCl_3$ - d_1 .

resorcinol using TFA, $AlCl_3$, and $BF_3 \cdot CH_3CH_2O_2$. No reaction occurred with either TFA or $AlCl_3$.

When $BF_3 \cdot CH_3CH_2O_2$ was employed, however, **3.12** and resorcinol cyclized to produce the C_{4v} -isomer of compound **3.16** (**3.16A**) in 20.6 % yield and the C_{2h} -isomer of

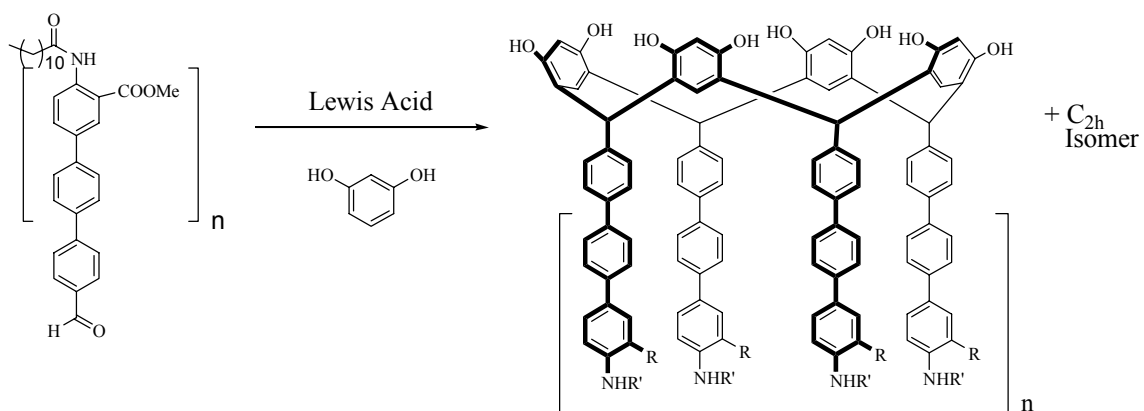


Fig. 3.9. General Lewis acid catalyzed synthesis of resorcinarene-oligophenylene compounds. $n=1,2,4$. $\text{R}=\text{COOMe}$ $\text{R}'=\text{CO}(\text{C}_{10}\text{H}_{23})$.

compound **3.16** (**3.16B**) in 54.4 % yield (cf. Fig. 3.10). (Characterization data for **3.16A** and **3.16B** is compiled in Tables 3.2 and 3.3, respectively, while the proton NMR spectra of these compounds are displayed in Figs. 3.11-3.14.) Likewise, aldehyde **3.15** condensed with resorcinol in the presence of $\text{BF}_3 \cdot \text{CH}_3\text{CH}_2\text{O}_2$ to produce the C_{4v} -isomer of compound **3.17** (**3.17A**) in 24.8 % crude yield and the C_{2h} -isomer of compound **3.17**

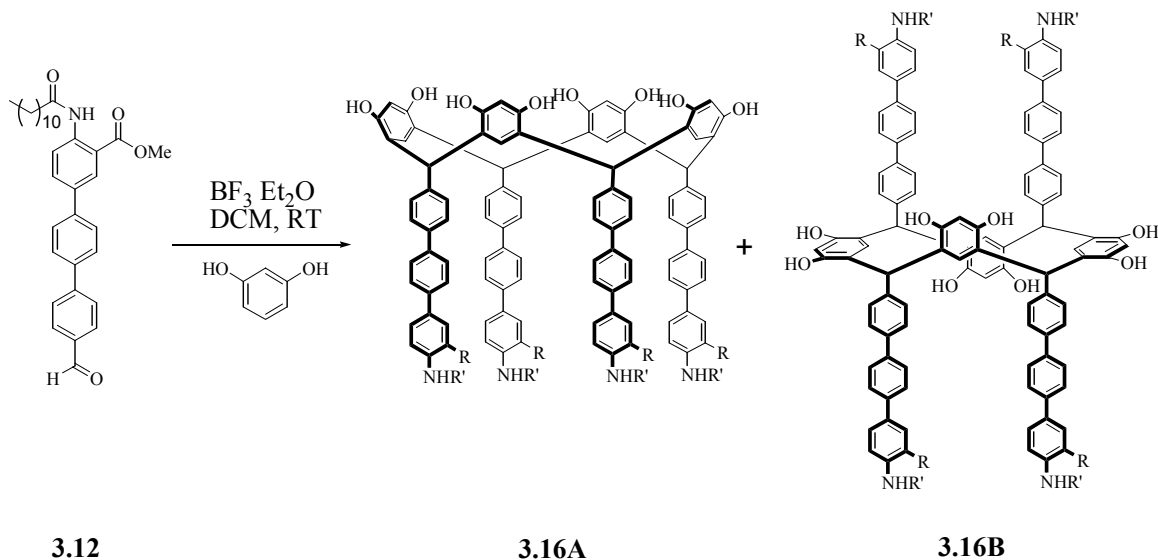


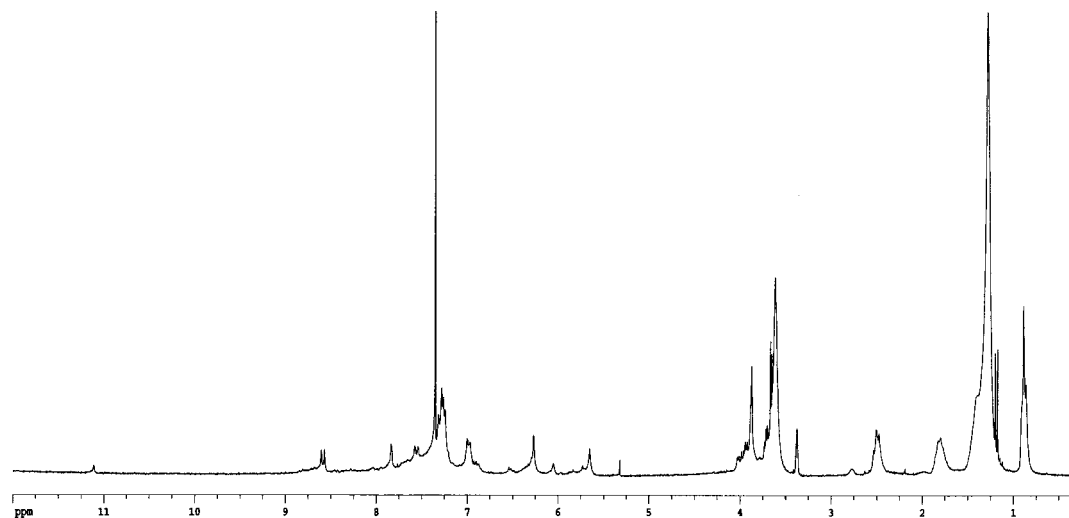
Fig. 3.10. Synthesis of the resorcinarene-oligophenylene compounds (**3.16A** and **3.16B**). $\text{R}=\text{COOMe}$ $\text{R}'=\text{CO}(\text{C}_{10}\text{H}_{23})$.

Table 3.2. Characterization Data for compound **3.16A**.

Technique	Conditions	Data
¹ H NMR	250 MHz Solvent = 10% MeOH-d ₄ : 90% CHCl ₃ -d ₁	δ 0.877 (t, 3 H), 1.28 (m, 14 H), 1.79 (p, 2 H), 2.51 (t, 2 H), 3.87 (s, 3 H), 5.65 (s, 1 H), 6.05 (s, 1 H), 6.27 (s, 1 H), 6.98 (d, 2 H), 7.28 (m, 6 H), 7.55 (dd, ⁴ J = 2 Hz, ³ J = 9 Hz, 1 H), 7.84 (d, ⁴ J = 2 Hz, 1 H), 8.59 (d, ³ J = 9 Hz, 1 H), 11.11 (s, 1 H)
MALDI-MS	Matrix = Anthracene	2421.26 obs. (M-H), (2423.05 calc'd)

Table 3.3. Characterization Data for compound **3.16B**.

Technique	Conditions	Data
¹ H NMR	250 MHz Solvent = 10% MeOH-d ₄ : 90% CHCl ₃ -d ₁	δ 0.877 (t, 3 H), 1.27 (m, 14 H), 1.40 (p, 2 H), 2.50 (t, 2 H), 3.88 (s, 3 H), 5.72 (s, 1 H), 5.83 (s, 0.5 H), 6.30 (s, 0.5 H), 6.52 (s, 0.5 H), 6.54 (s, 0.5 H), 6.89 (d, 2 H), 7.20 (m, 6 H), 7.55 (dd, ⁴ J = 2 Hz, ³ J = 9 Hz, 1 H), 7.83 (d, ⁴ J = 2 Hz, 1 H), 8.58 (d, ³ J = 9 Hz, 1 H), 11.11 (s, 1 H)
MALDI-MS	Matrix = Anthracene	2421.26 obs. (M-H), (2423.05 calc'd)

**Fig. 3.11.** Proton NMR spectrum of **3.16A** (250 MHz). Solvent is 10% MeOH-d₄: 90% CHCl₃-d₁.

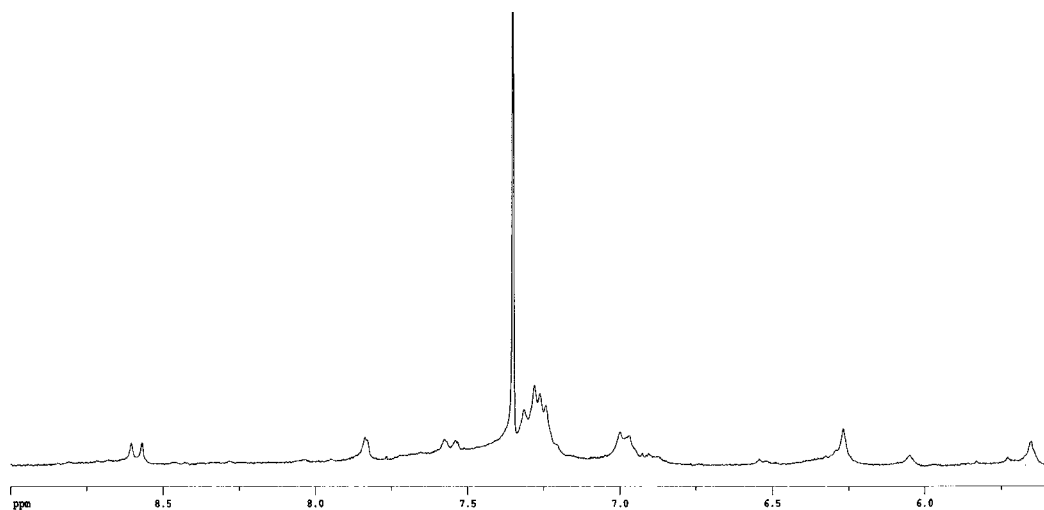


Fig. 3.12. Enlargement of the aromatic region of the proton NMR spectrum of **3.16A** (250 MHz). Solvent is 10% MeOH- d_4 :90% $CHCl_3$ - d_1 .

(3.17B) in 71.1% crude yield (cf. Fig 3.15). Since **3.17A** and **3.17B** are still not completely pure, only the NMR resonances in **3.16A** and **3.16B** will be assigned. Nonetheless, the proton NMR spectra **3.17A** and **3.17B** are shown in Figs. 3.16 and 3.17, respectively.

Since the C_{4v} and the C_{2h} compounds are structural isomers, compounds **3.16A** and **3.16B** both have calculated molecular weights of 2423.05 g/mol; similarly compounds **3.17A** and **3.17B** have molecular weights of 3263.96 g/mol. Conveniently, the masses of both isomers of compound **3.16** gave a parent peak of 2421.26 using MALDI-MS, while both isomers of compound **3.17** showed parent peaks of 3261.53 when the same method was employed.

Conclusions

This research group focuses on the synthesis of resorcinarene macrocycles for a variety of applications. One current area of interest is the use of resorcinarenes as

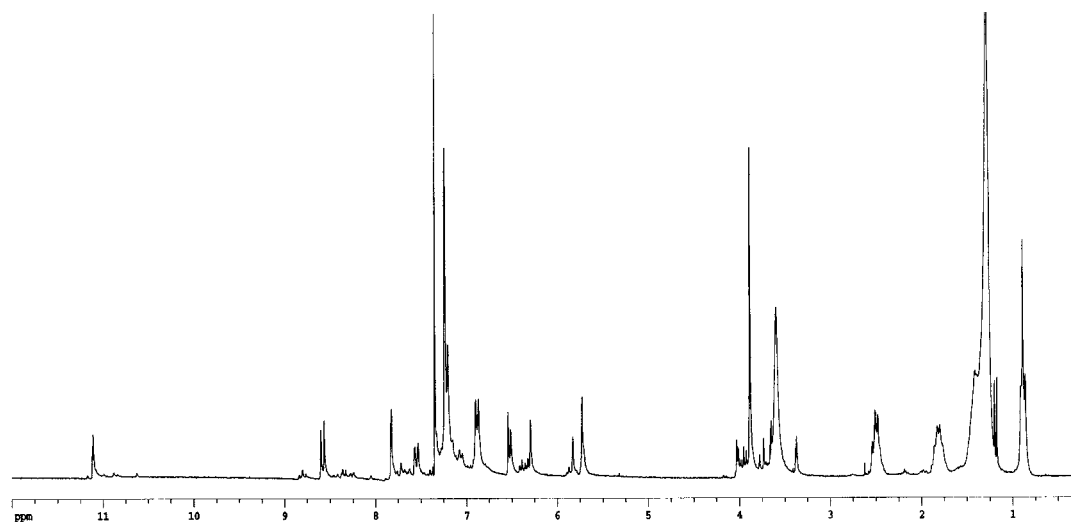


Fig. 3.13. Proton NMR spectrum of **3.16B** (250 MHz). Solvent is 10% MeOH- d_4 : 90% $CHCl_3$ - d_1 .

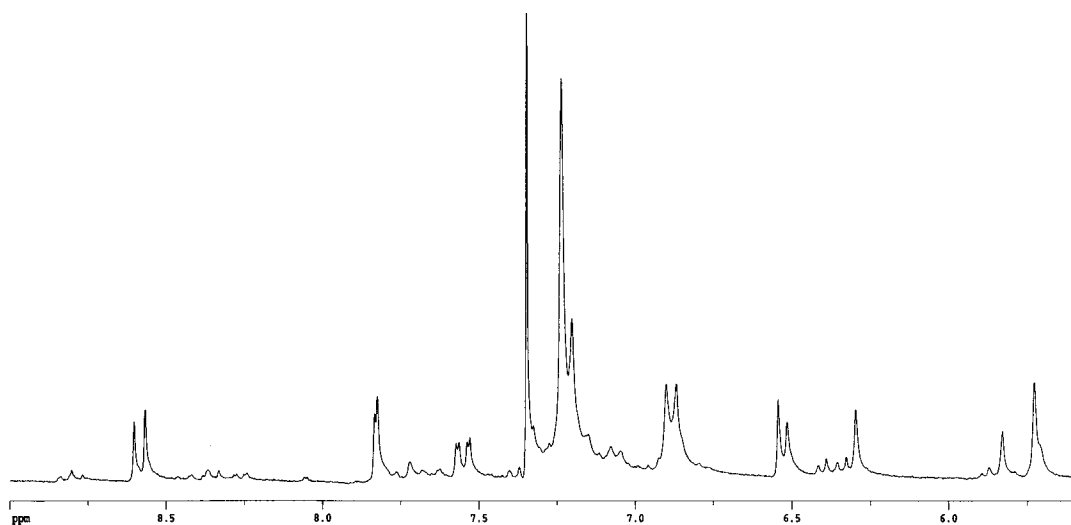


Fig. 3.14. Enlargement of the aromatic region of the proton NMR spectrum of **3.16B** (250 MHz). Solvent is 10% MeOH- d_4 :90% $CHCl_3$ - d_1 .

synthetic templates for covalently bonded tubular materials with a defined cavity diameter. Therefore, an account was presented of the design and synthesis of resorcin-

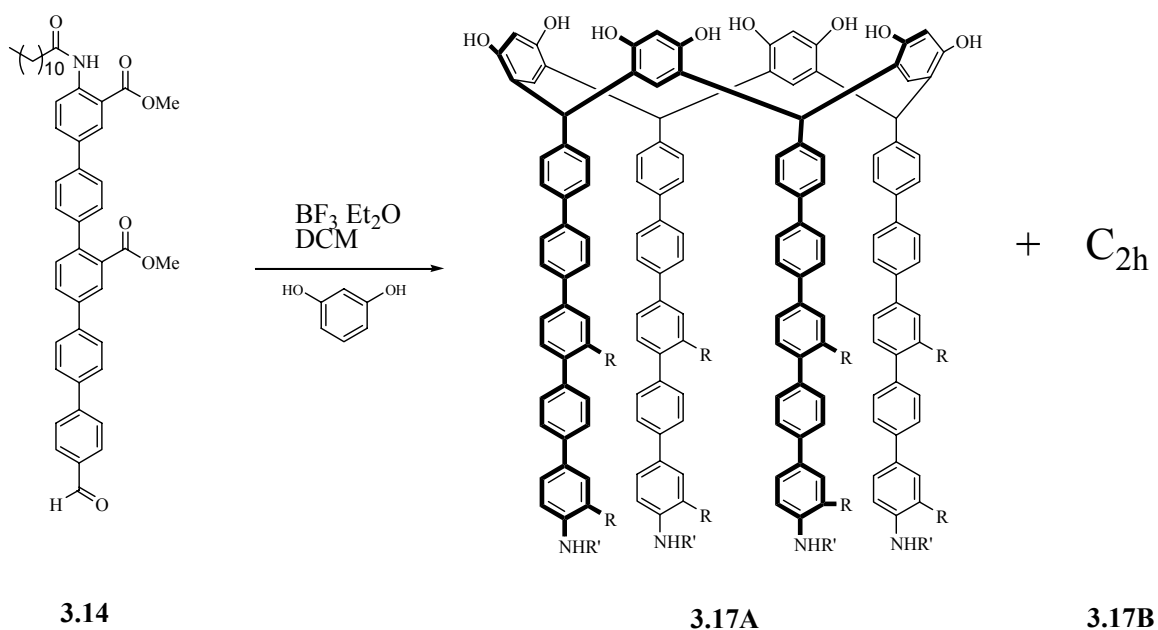


Fig. 3.15. Synthesis of the resorcinarene-oligophenylene compounds (**3.17A** and **3.17B**). R=COOMe R'=CO(C₁₀H₂₃).

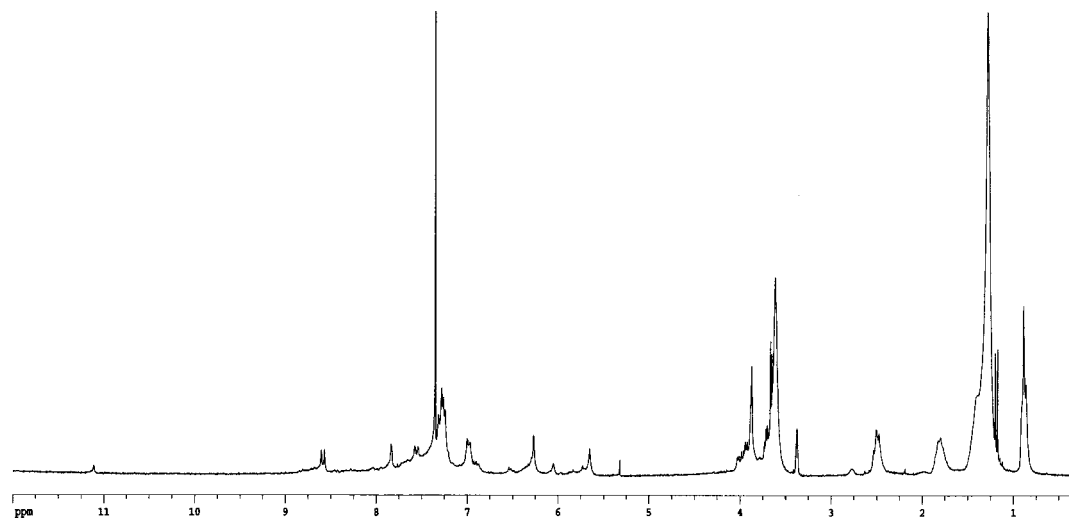


Fig. 3.16. Proton NMR spectrum of **3.17A** (250 MHz). Solvent is 10% MeOH-d₄: 90% CHCl₃-d₁.

arene macrocycles with both four dimeric and four tetrameric oligophenylene rods appended. In the process of condensing each of the oligophenylene aldehydes, two resorcinarene isomers (C_{4v} and C_{2h}) were produced (the structures of which were

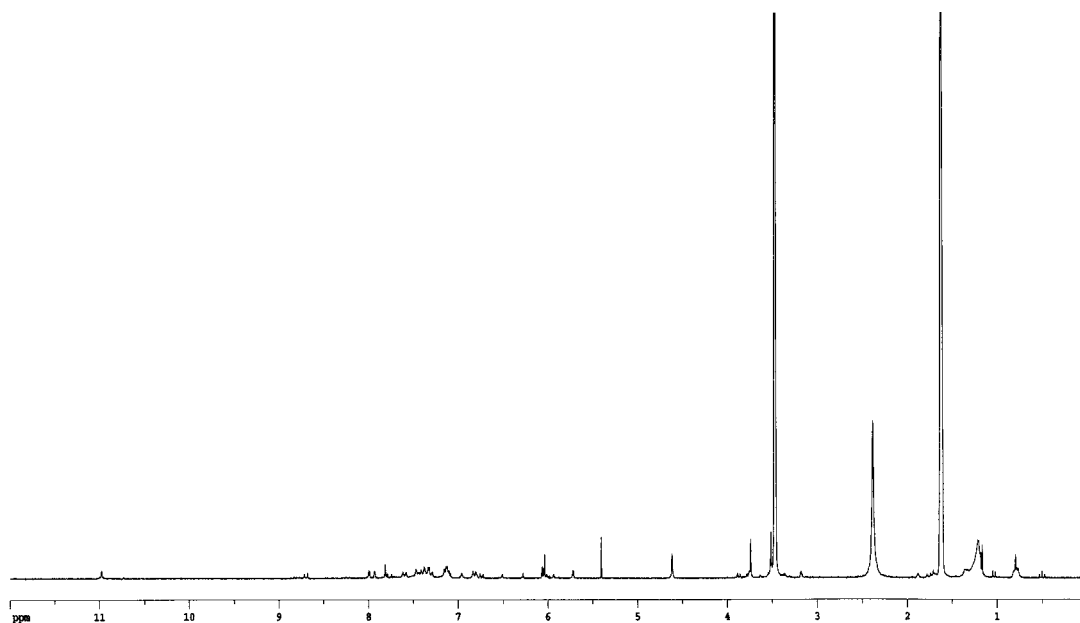


Fig. 3.17. Proton NMR spectrum of **3.17B** (250 MHz). Solvent is 10% MeOH- d_4 : 90% $CHCl_3$ - d_1 .

confirmed by proton NMR). As a continuation of this work, future synthetic work and properties studies in this facet of the macrocycle research are outlined below.

After successfully synthesizing the nonamer aldehyde, a condensation to produce a resorcinarene with four attached octameric oligophenylene rods has been planned (cf. Fig. 3.18). Similar to the resorcinarene-oligophenylene compounds with dimeric and tetrameric rods, the cyclization is expected to yield two resorcinarene isomers. Separation and purification of these isomers will then be necessary prior to full characterization.

Simultaneously, model studies will be undertaken to further probe potential applications of these three-dimensional molecules as hosts for organic phosphates. While

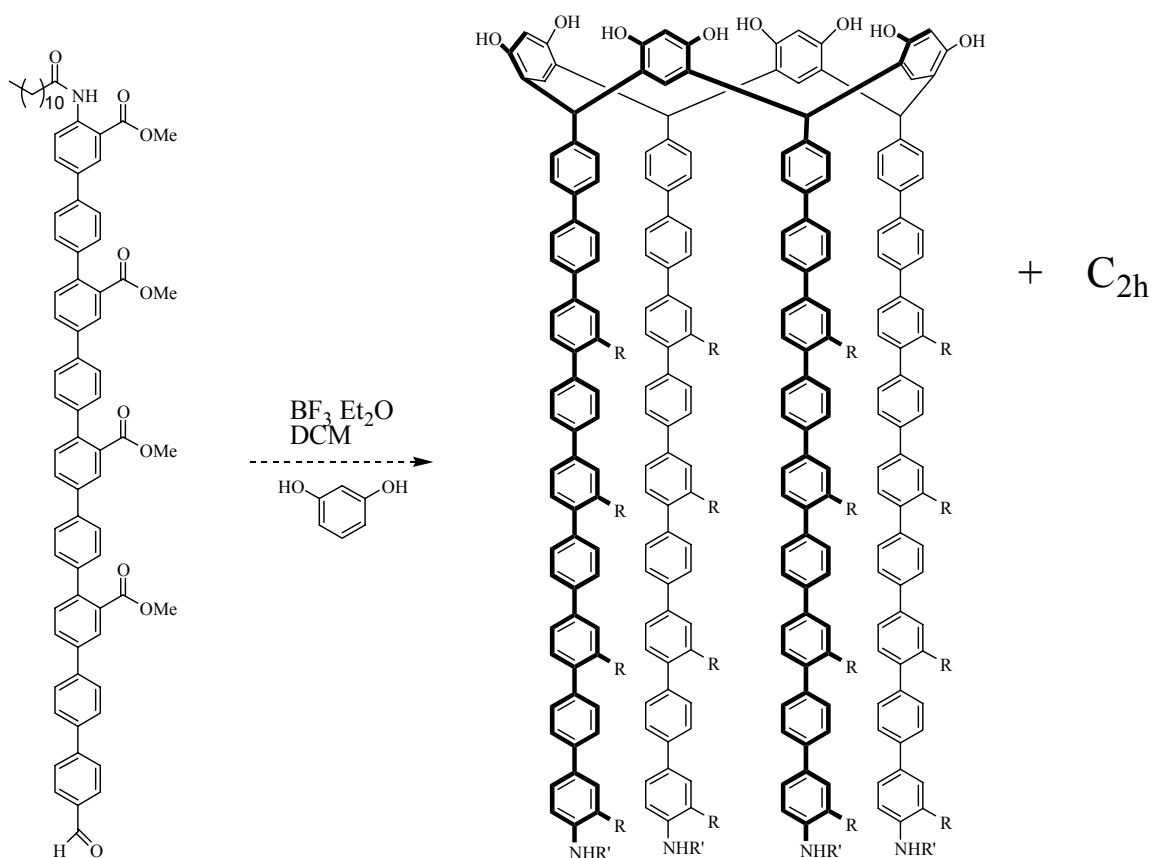


Fig. 3.18. Proposed synthesis of a resorcinarene-oligophenyl compound containing 40 phenyl units. $\text{R}=\text{COOMe}$ $\text{R}'=\text{CO}(\text{C}_{10}\text{H}_{23})$.

an eventual goal is to bind and sense LPA, other organic phosphates will be examined initially. Such phosphates will include both long and short chain alkyl phosphates as well as aryl phosphates. Studies will be undertaken to determine the binding constants of these modified resorcinarenes for various phosphate analytes, and, thereby, ascertain if the longer aromatic cavities created by the addition of progressively longer oligophenylene rods to the resorcinarenes have a significant effect on the ability of the resorcinarene-oligophenylene compounds to bind phosphates.

A long-term goal of this project has always been to crosslink the carboxylate side chains of the oligophenylene rods (attached to the resorcinarene macrocycle) through a Friedel-Crafts acylation reaction (cf. Fig. 3.19). Both trifluoro-methanesulfonic acid

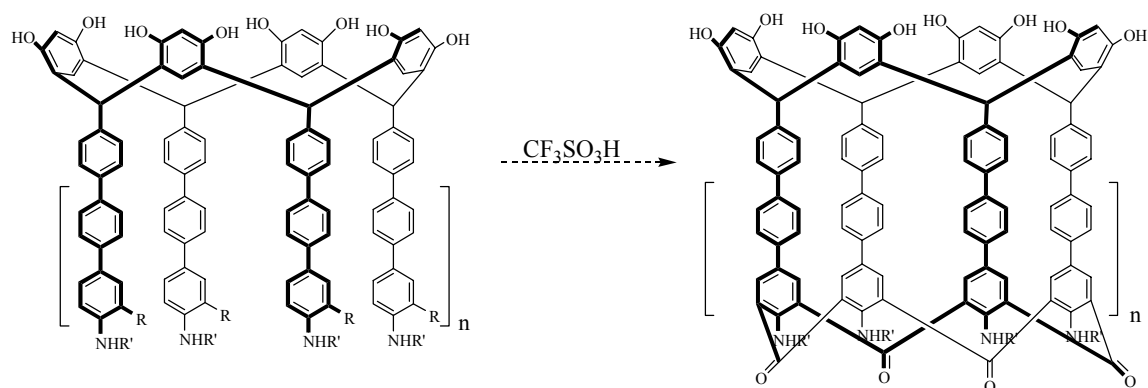


Fig. 3.19. Proposed cross-linking of the carboxylate side chains of the resorcinarene-oligophenylene compounds using a Friedel-Crafts acylation. $R=\text{COOMe}$ $R'=\text{CO}(\text{C}_{10}\text{H}_{23})$.

$(\text{CF}_3\text{SO}_3\text{H})$ ³⁰ and Lewis acids (i.e. AlCl_3) have traditionally been employed in such aromatic acylations. Crosslinking of the oligophenylene rods (whether fourfold or partial) would lead to a more rigid, tubular molecule with a well-defined hydrophobic pocket. We propose that these further modified resorcinarenes may be even more efficient binders of long chain alkyl phosphates and more durable artificial ion channels.

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Chapter 4. Conclusions

In this thesis, the use of resorcinarene macrocycles for a variety of biologically significant applications was explored. One such exploitation of the properties of these molecules, the detection and quantification of sugars and other saccharide analytes by tetraaryboronic acid resorcinarenes via UV-visible spectroscopy, was presented in Chapter 2. Specifically, the mechanism leading to a solution color change characteristic of each sugar, sugar phosphate, and sugar acid in the presence of the macrocycle was discussed in depth. Chapter 3 then described the addition of four oligophenylene rods to resorcinarenes to yield tubular materials with progressively longer aromatic cavities (depending on the length of oligophenylene used). These molecules represent potential artificial ion channels and/or hosts for a variety of large guest biomolecules.

The study of the mechanism by which our resorcinarene macrocycles colorimetrically detect sugars started in Chapter 2 with the selection of the model macrocycle **2.2**, which exhibited behavior similar to the tetramethyl resorcinarene macrocycle **2.1** in the presence of sugars, and represented a system with less variables (no boronic acids). Initial studies indicated that bond breaking and possibly macrocycle fragmentation occurred oxidatively through a radical pathway when **2.2** was heated in DMSO with no saccharides present. The synthesis of two model fragment compounds, **2.3** and **2.4**, was, therefore, undertaken as part of an effort to identify potential macrocycle fragmentation products.

The search for **2.3** and **2.4** amongst the products of the oxidation of **2.2** began by heating this tetramethyl resorcinarene to 140°C in DMSO while bubbling air through the solution. This oxidation generated a plethora of macrocycle fragments which were then

subjected to preparative scale HPLC isolation. Two fractions from this HPLC isolation (isolated from 18-20 minutes and 21-24 minutes, respectively) were of particular interest as they overlapped with the known retention times of **2.3** and **2.4** (18 and 23.3 minutes, respectively). Compound **2.3** was established as one of the fragments in the 18-20 minute isolate by proton NMR and MALDI-MS. Evidence of **2.4** among the many products in the 21-24 minute isolate was likewise found by MALDI-MS. Further work to locate the key resonances of **2.4** in the proton NMR of 21-24 minute isolate or otherwise confirm that **2.4** is a product of the oxidative fragmentation of the macrocycle **2.2** is necessary.

Based on the spectral evidence that indicated oxidative fragmentation of the resorcinarene **2.2**, a mechanism for the radical break up of the macrocycle by oxidation was proposed in the Conclusions Section of Chapter 2. Additional work by other members of the Strongin group will establish how the fragments of the resorcinarene interact with the saccharide analytes to cause the visually discernable color changes in solution. Once the exact mechanism of the sugar sensing by resorcinarene macrocycles is understood, work will begin on the synthesis of resorcinarene-based sensors which are designed to sense specific, biologically important sugar derivatives.

The synthesis of resorcinarene macrocycles with oligophenylene rods appended to the lower rim for the purposes of generating robust, covalently bonded tubular materials was also explored in this work. Through the addition of the oligophenylene rods to the resorcinarenes, we envisioned the creation of new materials that would embody the properties and utility of both resorcinarenes and oligophenylenes. Progress towards this goal was presented in Chapter 3 with a discussion of the synthesis of oligophenylene

rods containing 2, 4, and 8 phenyl units (compounds **3.3**, **3.7**, and **3.10**). An iterative molecular doubling approach was employed which used Suzuki couplings as well as no preparative scale chromatography or boronic acid isolations to maximize oligophenylene yields.

Upon successfully completing the synthesis of the oligophenylenes, two methods for incorporating the rods into resorcinarene-oligophenylene compounds were considered. A fourfold Suzuki coupling of each length of rod to the C_{4v}-isomer of a tetraarylboronic acid resorcinarene was initially planned; however, attempts to perform this fourfold coupling with the macrocycle and **3.3** and **3.7** separately were unsuccessful. Thus, another approach involving the addition of an aldehyde moiety to the oligophenylenes **3.3**, **3.7**, and **3.10**, followed by the condensation of each length of these modified rods with resorcinol, was considered. Chapter 3, therefore, continued with the presentation of the synthesis of the aldehyde containing oligophenylene rods **3.12**, **3.14**, and **3.15** via the Suzuki coupling of 4-formylbenzeneboronic acid to the brominated termini of **3.3**, **3.7**, and **3.10**, respectively.

With the synthesis of the oligophenylene rods with appended aldehydes complete, the next step was to condense these modified rods with resorcinol using a Lewis acid catalyst. The small scale condensation of **3.12** with resorcinol was attempted using the three Lewis acids AlCl₃, TFA, and BF₃·CH₃CH₂O₂ in separate experiments; however, only the condensation with BF₃·CH₃CH₂O₂ gave any products. Consequently, the large scale condensation of **3.12** with resorcinol was undertaken using BF₃·CH₃CH₂O₂ as a catalyst. This reaction yielded the resorcinarene-oligophenylene compounds **3.16A** and **3.16B** which were separated by flash chromatography and characterized by proton NMR

and MALDI-MS. The synthesis of the resorcinarene-oligophenylene compounds **3.17A** and **3.17B** was similarly performed via the $\text{BF}_3 \cdot \text{CH}_3\text{CH}_2\text{O}_2$ catalyzed condensation of **3.14** and resorcinol. While this synthesis was successful, further purification of the products is necessary for full characterization. Additionally, the condensation **3.15** with resorcinol is planned under similar conditions.

In conclusion, this work examined two potential applications of resorcinarene macrocycles. First, the mechanism by which tetraarylboronic acid resorcinarenes colorimetrically detect saccharide analytes was studied in an attempt to design more selective sugar sensors. Second, the synthesis of a new class of tubular materials was undertaken through the fourfold addition of various length oligophenylene rods to a resorcinarene scaffold.

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Appendix: Table of Chemical Vendors and Purities

Chemical	Vendor	Purity or Grade
Acetaldehyde	Aldrich	99%
Resorcinol	Lancaster	99%
Ethyl Alcohol (EtOH)	Aaper Alcohol and Chemical Company	95% USP
Concentrated Hydrochloric Acid	Fischer Chemical	Certified ACS Plus Grade
Sodium bicarbonate	Fischer Chemical	ACS Grade
Ethyl Acetate	Fischer Chemical	HPLC Grade
MgSO ₄	Fischer Scientific	Certified Anhydrous
Methyl Alcohol (MeOH)	Chem Central	Technical Grade
Dichloromethane (DCM)	Delta Distributors	Technical Grade
2',4'-dihydroxyacetophenone	Aldrich	99%
Zinc Chloride	Aldrich	99.999% Anhydrous
T-Butyl Nitrite	Aldrich	90% pure 10% T-Butyl alcohol
Benzene	Fischer	ACS Grade
I ₂	Aldrich	99.99+
Hexanes	Delta Distributors	Technical Grade
4-Formylbenzene boronic acid	Aldrich	Contains varying amounts of anhydride
K ₂ CO ₃	Mallickrodt	Anhydrous, ACS Grade
Pd(PPh ₃) ₄	Aldrich	99%
Dimethylformamide (DMF) (Anhydrous)	Aldrich	99.8%
DMF (Hydrous)	Fischer	ACS or Sequencing Grade
BF ₃ ·ETO ₂	Aldrich	Purified, Redistilled
Chloroform	Aldrich	99.8%

Vita

Patricia Anne Beck was born on September 8, 1976 in Neenah, Wisconsin to Dr. Guy W. Beck and Ruth E. Beck. After moving several times within Wisconsin, she graduated from Berlin High School (Berlin, Wisconsin) in 1995. She then matriculated at Ripon College and received a bachelor of arts degree in chemistry in May of 1998. In August of 1998, she began her graduate studies in chemistry at Louisiana State University under the direction of Dr. Robert M. Strongin (Associate Professor of Chemistry, Louisiana State University).